Study Title: A Real-World, In-Situ, Evaluation Of The Introduction And Scale-Up Of Robot-Assisted Surgical Services In The NHS: Evaluating Its Impact On Clinical And Service Delivery, Effectiveness And Cost (the REINFORCE study).

Multi-centre Service Evaluation Protocol

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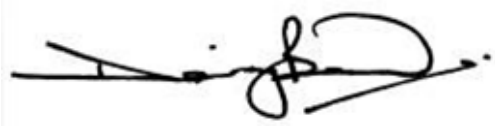

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2. LAY SUMMARY

What is this study about?

This study (known as REINFORCE) aims to work out if robot assisted surgery, a relatively new development, should be routinely available in the NHS and also to assess any barriers to its implementation.

Why this Study?

Over the next 20 years, surgery performed with the help of a robot (called "robot-assisted surgery") is expected to increase rapidly around the world, especially for cancer conditions. Previous research shows that when robot-assisted surgery has been introduced in some clinical areas, like urology, it can help surgeons be more precise and can reduce a patient's hospital stay. Using robot-assisted surgery may also speed up training for surgeons to enable them to become experts more quickly. However, robot assisted surgery has not been tested in all clinical areas and is very expensive with each robot costing over £1million). Also, when robot-assisted surgery is introduced into hospitals it requires special consideration as the set-up can be disruptive. The robot can take up a lot of space requiring physical modifications to operating theatres. The surgeons and the wider surgical team have to change how they operate, and the way patients move through their patient journey also has to change. It is not yet clear whether the benefits to patients or the health system of doing surgery this way is worth the cost and the disruption. The REINFORCE study aims to answer that question and provide guidelines for the best way of doing it if robotic surgery is shown to be useful.

How will the study be done?

We have designed the study to be able to measure the impact of robot-assisted surgery as it is introduced in the UK and scaled up in other hospitals currently performing robotic surgery but planning to expand services. It will study the effects of robot assisted surgery as it is rolled out at different sites in a planned way. It will measure the safety and benefit of the new treatment as it is being rolled out. We will measure what happens to patients who get robot-assisted surgery as part of the service and compare their outcomes (e.g., complications, recovery time) to conventional surgery. We will also track how introducing robot-assisted surgery impacts on the staff and the surgeons, and how it affects wider care in hospitals across the country. We will also work out how much robot-assisted surgery really costs and whether the benefits are value for money.

Who has been involved in the design of the study?

We have consulted widely about how best to design the study. Patients, surgeons, nurses, NHS managers, scientists, and industry have been involved and will continue to advise on this study. We will involve patients throughout the study period.

How will the results of this study be used?

This study will provide the NHS the information needed on the benefits of robot-assisted surgery and how it affects the wider health system. It will help decide whether the benefits of robot-assisted surgery are worth the cost and the disruption to services and whether robot-assisted surgery should be available routinely in the UK. It will also provide important guiding information on how best to provide robotic surgery, if found to be useful.

Who are the study team?

We have assembled a team of surgeons, researchers, patient partners, economists, NHS commissioners and managers. The team has a very strong track record of working together in this type of study, especially providing decision making information for the NHS.

3. SYNOPSIS

Study Title	A Real-World, In-Situ, Evaluation Of The Introduction And Scale-Up Of Robot-Assisted Surgical Services In The NHS: Evaluating Its Impact On Clinical And Service Delivery, Effectiveness And Cost (the REINFORCE study)
Study registration	ISRCTN: (include date of reg)
Funder	National Institute of Health Research Health Services and Delivery Research (HS&DR) Programme NIHR Evaluation, Trials and Studies Coordinating Centre University of Southampton Alpha House Enterprise Road Southampton SO16 7NS netsmonitoring@nihr.ac.uk 023 8059 5586
Study Design	A stepped-wedge evaluation (or multiple interrupted time series if operational constraints apply) with integrated process evaluation and economic assessment
Study Participants: Stepped-wedge evaluation	**Study sites:** NHS hospitals planning to introduce/expand Robot Assisted Surgery (RAS) services. Sites will be switched over from non-RAS to RAS-augmented services (or switch up from one level of provision to another) in a random order. **Study participants:** All patients undergoing the index procedure (RAS or otherwise) at each site across all time periods of the study. The project is embedded in normal NHS care and it is intended to be non-selective (all patients undergoing surgery for the index procedure are candidates).
Process evaluation	**Study participants:** Three key personnel including surgeons, theatre staff and service managers will be sampled from 6 REINFORCE sites and invited to interview. Additionally, 3-4 commissioners will also be interviewed and sampled from across the suite of trial sites. The sample size overall will be approximately 40 interviews.
Sample Size	2,560 procedures
Planned Study Period	01 January 2022 – 31 March 2025 (39 months)
Planned Recruitment period	01 July 2022 – 01 July 2024 (or earlier if NHS operational constraints apply)
Objectives	• Impact of RAS system transformation on clinical and service delivery

	• Budget impact and cost-effectiveness to the NHS of the introduction of RAS at scale • Potential benefit and harms of RAS across and within specialty areas • Mechanisms of change underpinning any change in outcome, including surgeon training
Outcome Measures	Outcome measurement include outcomes included in the recently reported RoboCOS core outcome set (1). **1. Patient-level/clinical outcomes:** a. Patient benefit (as measured by the normalised procedure-specific patient reported outcome [specialty specific PROM] at 3 months) b. Length of stay c. Time to recovery to normal activities d. Complications (as measured by the Clavien-Dindo measure of surgical complications) e. Peri- and post-operative complication frequency f. Quality of life (as measured by EQ-5D-5L) g. Patient experience **2. Organisational-level outcomes:** a. Cost-effectiveness b. Re-admission rates c. Resource use d. Overall cost of care e. Impact on waiting lists f. Impact on workforce 3. **Surgeon/team outcomes**: a. Surgical precision b. Operative control c. Operative visualisation d. Team communication* e. Surgical training (for consultants)* f. Ergonomic impact* 4. Population a. Equity of access * These will primarily be explored in the process evaluation

4. ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
GCP	Good Clinical Practice
GI	Gastro-Intestinal
GP	General Practitioner
HS&DR	Health Services and Delivery Research Programme
ICF	Informed Consent Form
NHS	National Health Service
NIHR	National Institute for Health Research
NoMAD	Normalisation MeAsurement Development tool
NPT	Normalisation Process Theory
OKS	Oxford Knee Score
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
RAS	Robotic Assisted Surgery
R&D	NHS Trust R&D Department
SOP	Standard Operating Procedure

5. BACKGROUND AND RATIONALE

Surgery is an essential part of healthcare provision with an average of 8 million patients undergoing a surgical procedure in the UK every year (over 12,000 procedures per 100,000 population costing £11 billion)(2). However, not all new surgical procedures and innovations are evaluated as much as they should be before widespread use in the NHS, both from a health service delivery and an efficacy/safety perspective. Robotic Assisted Surgery (RAS) has the potential to provide high performance and increased access to services for the population, particularly for cancer surgery and other effective high-volume procedures such as arthroplasty; however, the impact of RAS on healthcare service provision is unclear.

Robotic Assisted Surgery

The 2019 Royal College of Surgeons (RCS) England Future of Surgery report outlined how surgery is likely to change in the NHS over the next decade with major predicted expansion in the provision of RAS (3). The Topol Review exploring the impact of a digital future on the NHS came to similar conclusions (4). The potential benefit of increased RAS provision in a post-COVID world has also been noted with the

potential to address substantially expanded waiting lists (5). It is thought that RAS reduces variation in both surgical performance and the invasiveness of interventions and therefore improves outcome in terms of surgical objective, complications, and speed of recovery. RAS also has potential health (ergonomic) benefits for the surgeon linked to reduced sick leave and improved longevity of service (6). The format of surgery is entirely different to conventional surgery with efficiency of service delivery being a key component - the delivery of surgery involving skilled surgical technicians undertaking some procedures under the supervision of a surgeon. Coupled with electronic data capture, virtually augmented in theatre expertise, and 3D device printing, there is set to be a technological revolution in the delivery of surgical healthcare of which RAS is a key component.

The RCS report stressed the imperative that RAS, like all surgical innovations but especially because of its wider impact on the service, be rigorously evaluated for safety, effectiveness and impact on services before widespread uptake.

Current Evidence

Some evaluation of the clinical benefits of robot assisted surgery has been undertaken, especially in urology (7, 8). The case for RAS is well made for a number of urology procedures which has seen reduced invasiveness of complex surgical interventions with improved outcomes and reduced variability in surgical performance. In 2012, NICE recommended RAS for the management of radical prostatectomy (9) and urology has since enjoyed improved equality of access for the population to high quality surgery. Outside urology there has also been expansion but evidence to support RAS, particularly in non-urological areas and to inform wider roll-out of RAS, is sparse. Systematic reviews and meta-analyses of safety and efficacy of RAS exist but these tend to compare RAS against standard endoscopic surgery and with relatively convenient and accessible outcomes such as operation duration, complications, and recovery time (10-12). Whilst mostly safe, the majority of the work to date has highlighted continued uncertainty for the effectiveness and usefulness of RAS. Specialties with a less mature RAS background, such as gynaecology and thoracic surgery are even further limited in terms of evidence for benefit (13, 14).

This limitation became apparent at an RCS workshop organised under the “Future of Surgery” planning. In response, the first pan-specialty systematic review of RAS which included all RCT comparisons and all outcomes was conducted (15). A comprehensive search of MEDLINE, Embase, Cochrane CENTRAL, Scopus and Web of Science Core Collection was conducted from 1 January 2008 to 23 August 2019 (7142 studies screened of which 413 titles underwent full-text review resulting in the inclusion of 183 reports of RCTs (representing 76 unique study populations). This showed that over the past 10 years, only 2% (183/7116) of the RAS evaluation literature is based on randomised evidence. Almost all trials were

small, underpowered and had high levels of duplicate sampling. Overall, the research quality was poor. It concluded that while there was no immediate concern on safety, there is little evidence to make any strong conclusion on effectiveness of RAS to inform system-wide change. The RCS report re-iterated this lack of evidence and stressed the urgent need for more evaluation.

The systematic review (15) further highlighted the heterogeneity of outcomes that had been used to assess the clinical effectiveness of RAS to date (compounding problems with the usefulness of the previous literature). To address this we sought funding to develop of a core outcome set (RoboCOS) for the service level assessment of RAS (1) The core outcome set work highlighted that, for a service level evaluation to be most informative, outcomes must be measured at multiple levels including at the: a) patient/clinical level; b) surgeon/team level and c) organisational level and d) population level (see outcomes section below).

More significantly, there has been very little research to date on how RAS impacts wider service delivery. One study (by Randell et al.,) conducted alongside the ROLARR trial of RAS for rectal cancer provided early insights (16, 17). It showed that issues at surgeon, operating team and system level can affect system performance and clinical outcome and that the impact on the system can be problematic if implementation is not rigorously pre-planned. It recommended further research be done to explore what system/team level factors might affect the effectiveness of RAS in wider surgical indications (17).

6. AIM AND OBJECTIVES

This study aims to undertake a real-world, large-scale evaluation of the introduction and scale-up of RAS services evaluating its impact on NHS service delivery, clinical effectiveness, budget and cost-effectiveness. Specific objectives are to provide evidence on the:

1. impact of RAS system transformation on clinical and service delivery
2. budget impact and cost-effectiveness to the NHS of the introduction of RAS at scale
3. potential benefit and harms of RAS across and within specialty areas
4. mechanisms of change underpinning any change in outcome, including surgeon training

7. STUDY DESIGN

REINFORCE is planned as a multi-centre stepped-wedge evaluation (with integrated process evaluation and economic assessment) of the introduction and scale-up of RAS services in the NHS. The stepped-wedge approach provides a framework for a structured roll-out and evaluation. The design will allow a staged evaluation collecting data before and after an intervention (change in service delivery) as the change is phased in gradually in an ordered sequence.

Study sites will be those NHS hospitals planning to introduce/expand RAS services (RAS provision costs are thus covered). Sites will be switched over from non-RAS to RAS-augmented services (or switch up from one level of provision to another) in a random order.

Stepped wedge trials (SW-RCTs) are known to provide an ideal option for the evaluation of interventions at a service level and for assessing interventions as they are rolled-out in practice (18). Data are collected over several time periods, allowing the impact on clinical and service delivery to be evaluated over time. Recognising the different levels of maturity of RAS provision across the NHS, the evaluation will address both RAS-naïve sites who have plans to introduce RAS to their clinical service and existing RAS-active sites who are scaling up RAS to new specialties/new procedures.

This real-world design is known to be complex and many previous such studies have reported implementation issues such as the intended pattern of roll-out not occurring according to plan (such as an unexpectedly significant number of sites needing to convert at times outside the design due to operational issues or policy changes). We have incorporated a pre-planned contingency for this eventuality which would be to treat sites as multiple interrupted time series with each site analysed individually and results pooled (see analysis section below).

Process Evaluation

The use of process evaluations in trials of complex interventions has become a useful tool to facilitate the understanding of many aspects of trial conduct, including intervention implementation, and to aid interpretation and understanding of trial outcomes (19). Existing guidelines for conducting process evaluations of complex interventions emphasise three components as important for understanding how outcomes are achieved: implementation; mechanism of impact; and context and these have guided the design of this REINFORCE process evaluation (19).

Differential implementation of a service change (such as adoption of RAS) at system/local levels can affect the rate of adoption and therefore, context can influence outcomes in trials (20, 21). In addition, within stepped-wedge trials outcomes can be clustered by site and the process evaluation can incorporate adjustments for such clustering. This will allow us to explore further elements such as whether choice of site had an influence, and whether site characteristics shaped the adoption and the delivery of the RAS service (22). Therefore, the aim of the process evaluation is to understand the implementation and/or scaling up of RAS (from a service perspective) at sites and whether and how variations in implementation across sites (i.e. context) influence trial outcomes (i.e., mechanism of impact).

The specific objectives are:

1. To *assess plans for implementation and adoption* at sites by identifying and investigating perceived challenges and solutions to RAS adoption pre-switchover;
2. To *explore the immediate impact of introduction* of RAS by assessing any change to process during the transition phase of implementation delivery at system, surgeon, and patient level i.e. any changes to clinical pathway, staff mix, or expertise required, surgeon ergonomics, impacts on patient satisfaction;
3. To *assess the impact of learning (new and existing) and speed of roll out and adoption* by identifying realised opportunities and failures post-switchover to RAS;
4. To *determine whether effectiveness varies between sites*, and if so, establish how individual site characteristics (including processes) are associated with effectiveness.

The process evaluation has been informed by previous in-depth explorations of RAS particularly the work of Randell et al (a realist evaluation) (16) and REINFORCE-WP1 which has applied behaviour change frameworks to understand implementation of RAS. Findings from these studies will guide further focussed exploration within the process evaluation, which will draw on Normalisation Process Theory (NPT) to guide data collection, analysis and interpretation (23). NPT is an appropriate guiding theory for this process evaluation given its ability to aid understanding of implementing, embedding, and integrating new technologies and or complex interventions.

8. OUTCOMES

For this evaluation, the following outcomes are included, and have the RoboCOS core outcome set as their starting point:

1. **Patient-level/clinical outcomes:**
    a. Patient benefit (as measured by the normalised procedure-specific patient reported outcome [specialty specific PROM] at 3 months)
    b. Length of stay
    c. Time to recovery to normal activities
    d. Complications (as measured by the Clavien-Dindo measure of surgical complications)
    e. Peri- and post-operative complication frequency
    f. Quality of life (as measured by EQ-5D-5L)
    g. Patient experience

2. **Organisational-level outcomes:**

a. Cost-effectiveness
   b. Re-admission rates
   c. Resource use
   d. Overall cost of care
   e. Impact on waiting lists
   f. Impact on workforce

3. **Surgeon/team outcomes**:
   a. Surgical precision
   b. Operative control
   c. Operative visualisation
   d. Team communication*
   e. Surgical training (for consultants)
   f. Ergonomic impact*

4. **Population:**
   a. Equity of access

* These will primarily be explored in the process evaluation

Normalised procedure-specific patient reported outcome: It is widely recognised that procedure/disease-specific measures of patient outcome are more sensitive to changes in direct patient benefit compared with more generic measures of quality of life such as the EQ-5D-5L (19). As this evaluation includes index procedures from more than one specialty, it will necessitate the use of more than one disease or specialty specific patient reported outcome measure (PROM). For example, the Gastrointestinal Quality of Life Index (GIQLI) for upper GI conditions (20) or the Oxford Knee Score (OKS) for knee replacement (21). The raw post operative outcome scores for each sub-specialty assessment (on individual patients) will be normalised onto a notionally common scale ahead of the study analysis to allow summation and comparison across procedures.

For the sample size calculation (see below), we have used patient benefit as the “primary” outcome, as they generally require the highest sample size to detect meaningful change accepting that outcomes at each level are equally important.

9. PARTICIPANT IDENTIFICATION

9.1. Study setting

The study will be conducted in secondary care NHS hospitals across the UK at sites planning to introduce/expand RAS services. We will recruit participating sites from institutions that are 1. Procuring new RAS equipment (naive sites) 2. Sites that already utilise RAS but are considering a change in specialty or procedure using RAS methods.

9.2. Study Participants

Site level:

We will recruit 16 sites to the study across a range of specialties e.g., Urology, Colorectal, Thoracic, Gynaecology, Orthopaedics, Upper Gastro-Intestinal (GI). This will include approximately 6 RAS naïve sites introducing a RAS-augmented service, and approximately 8-10 more mature RAS sites which will be scaling up RAS services to new specialties/procedures (reflecting the current penetration of RAS services across the NHS at this time). Each site will identify an "index procedure" (e.g. radical prostatectomy for RAS-naïve sites introducing RAS to their urology service) for which a RAS operative approach is to be introduced. All surgeons performing the index procedure at the recruited site will be included. Surgeons will have undergone training in RAS prior to site conversion.

Patient level:

All patients undergoing the index procedure (RAS or otherwise) at each site across all time periods.

Inclusion and exclusion criteria

The project is embedded in normal NHS care and it is intended to be non-selective (all patients undergoing surgery for the index procedure are candidates). There are no exclusions for geographical location, age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity.

We will attempt to overcome any site selection bias by seeking to include sites with as wide geographical variation as possible (and by examining several surgical specialties) but we will be restricted to sites that have already agreed to purchase and install RAS systems or have mature RAS systems in place. Appropriate representation of industry in the supply of RAS equipment will also be accommodated within site selection.

10. PROTOCOL PROCEDURES

10.1. Recruitment

Site Recruitment

We will recruit participating sites from NHS institutions that are 1. Procuring new RAS equipment (naive sites) 2. Sites that already utilise RAS but are considering a change in specialty or procedure using RAS methods.

The study will be conducted across six specialties for which RAS is currently an option for routine procedures: Urology, Colorectal, Orthopaedics, Gynaecology, Upper Gastro-Intestinal and Thoracic surgery. To capture the effect of introducing RAS at different levels (new site, new specialty or new procedure) a specified "index" procedure within each site will be identified as the focus for the evaluation. The index procedure will be a surgical procedure which has not previously been RAS-enabled in that site. All surgical provision for each index procedure will be tracked before the introduction of a RAS-augmented service (the control phase) and then after RAS is introduced (the intervention phase) over the 2-year recruitment phase. Exemplars of possible index procedures are shown in Table 1. below (using urology and colorectal surgery as a specialty examples) – they will be finalised with each site when they are formally enrolled in the study.

Table 1.

Type of site	Exemplar index procedure
• No previous RAS provision in any specialty	Radical prostatectomy (performed by RAS in Urology surgery for the first time at that site)
• RAS established in one specialty (urology) commencing service for new specialty (colorectal)	Low anterior resection (performed by RAS in colorectal surgery for the first time at that site)
• RAS established commencing new procedure within specialty (urology)	Partial nephrectomy (having previously only performed RAS prostatectomy)

As outlined in section 7 above, all surgical provision for each index procedure will be tracked before the introduction of a RAS-augmented service (the control phase) and then after RAS is introduced (the intervention phase) over the 2-year recruitment phase.

Patient recruitment, consent and data collection

We will register participants over a two year period (planned from July 2022 (or earlier if NHS operational constraints apply) through to July 2024). All patients undergoing surgery for the stated index procedures will be invited to contribute and share their data with registration. Patient care will be unchanged from routine pathways and procedures at the recruited institution (albeit with new RAS specific ones once instigated). All patients undergoing the index procedure (RAS or otherwise) at each site across all time periods will be eligible and the number of eligible patients will be recorded throughout the study period.

Patients will be verbally informed about the routine data collection aspect of the study at the consultation when they are listed for surgery. An information leaflet on the study will be available. In addition to the routine data collection, patients will also be asked if they would complete questionnaires (ideally electronically or paper based as desired) before the operation (baseline) and 3 months post operation.

The Baseline questionnaire will be completed prior to the patient's surgery at a routine care outpatient / pre-admission surgical clinic visit prior to surgery or on the day of surgery. The questionnaire would include a specialty specific patient reported outcome measure (PROM) and a general quality of life measure. The questionnaire is not onerous and will not involve an extra visit. If the patient is unable to complete in clinic an electronic version can be sent to the patient following consent. At this time point patient demographic data will also be collected. Patients will also be asked for their preferred mode of follow-up whether by mail or electronically. For patients would do not wish to complete the questionnaire component of the study only the routine data and minimal demographic data (ethnicity, sex, date of birth) would be collected.

The follow-up questionnaire will be sent to participants at 3-months post-surgery. The questionnaire would include a specialty specific patient reported outcome measure (PROM), general quality of life measure, patients experience and health resource questions. These will be sent by the central study team and can be completed by post or online, depending on patient preference.

Reminders via e-mail, post and telephone to participants who do not respond to the initial request for follow-up data will be coordinated by the central study team.

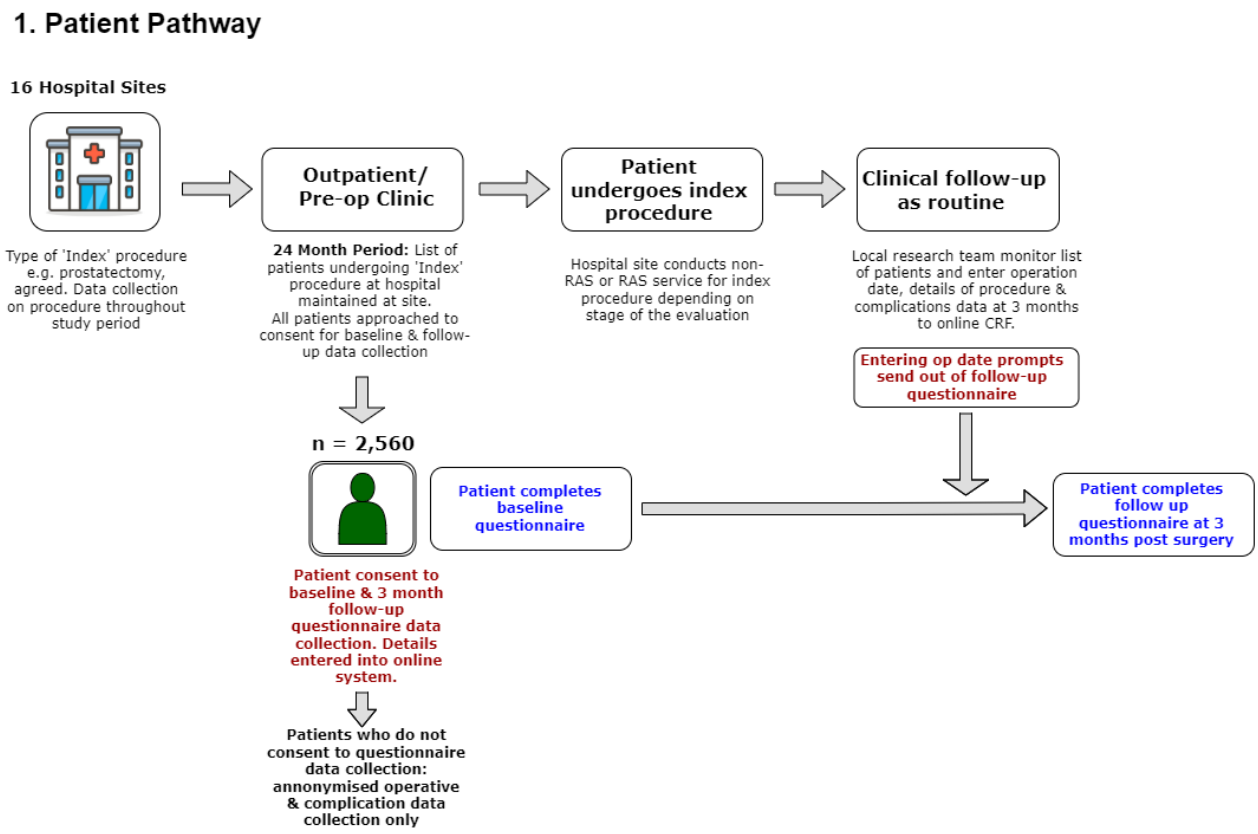
All other evaluation information will be collected as part of the standard clinical pathway. Routine data from the surgery admission, such as, operation date, complications, length of stay and interoperative resource will be collected by local study team on a case report forms (CRF) and entered on the study database. Data on any complications up to 3 months post-surgery would also be captured and entered

on the database. This data would be completed on the day of surgery or taken from medical records retrospectively by local research nurse/staff. Depending on the volume of procedures at a site it is anticipated that this retrospective review will be conducted every 2 weeks to capture the surgery data and 3-month review e.g., complications etc.

In addition, following each surgical procedure a questionnaire related to conducting the procedure e.g. questions on visualisation etc. will be completed by the surgeon who carried out the procedure.

An overview of the patient pathway is detailed in Figure 1 and a data collection flow chart outlined in Appendix 1.

Figure 1.



10.2. Informed Consent

This is a service-level evaluation of the addition of RAS to the spectrum of surgical services at sites. Patients are not being randomised to one treatment or another. Patients will, as standard practice, be asked to consent to the type of surgery planned for their care. Consent will also be sought for collection of data for this study and for the completion of patient reported outcomes during both control and intervention periods.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

Written Informed Consent will then be obtained by means of participant-dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

10.3. Randomisation

There is no randomisation of patients within this study. The anticipated overall order in which sites transfer over to RAS enabled services will be randomised at the start of the recruitment period (although as outlined above as the study is dependent on operational constraints such as procurement and implementation of RAS services outside the study needs, randomisation of sites may not be possible). The randomisation schedule will be constructed by an independent statistician blinded to the identifying site details.

11. Process Evaluation

Methods

Overall study design

This is a mixed-methods process evaluation that will collect data sequentially both with respect to the data type (e.g. quantitative data from surveys and qualitative data from interviews) and the timing of the phase of intervention switchover (pre-, transition, post-the introduction of RAS at each site. The data will be weighted equally and mixed by connecting the data during analysis, from the process evaluation itself but also the trial in which it is embedded (i.e. effectiveness outcomes). The process evaluation will involve interviews and surveys. The most informative 'process' phases are the periods immediately pre and post switchover to a RAS-augmented service (24). Therefore, we will target data collection over the transition phase (immediately before, and at least the first two periods after, switchover at each site). For the purposes of research objective 1-3 listed above (Section 7) the methods will be as specified below but also allow some flexibility in order to be responsive to emergent issues within the study.

Sampling

- Surveys: Staff involved with REINFORCE at study sites (n=16) will be invited to complete a study questionnaire at pre-, switch over, and post switch over time points. Included staff will involve anyone involved in the RAS pathway such as surgeons, theatre staff, managers, etc. Consent will be implicit by completion and return of the questionnaire.
- Interviews: Three key personnel including surgeons, theatre staff and service managers will be sampled from 6 REINFORCE sites and invited to interview. Sites will be sampled purposively likely based on differences across the implementation pathway i.e. naïve, early, and late. Participants will be invited by the Trial Manager/Chief Investigators and asked to contact the relevant Research Fellow for further information. Interview participants will be provided with an information sheet and provided with an opportunity for any questions to be answered before verbal consent is sought. Interviews will be conducted at both pre and post switch over time points, and within the same individuals, providing a total sample of 36 site-based interviews. Additionally, 3-4 commissioners will also be interviewed and sampled from across the suite of study sites. The sample size of approximately 40 interviews has been guided by the pragmatic principles of information power (25). Information power proposes that the relevance of the information held within the sample determines the size i.e. greater relevance = smaller sample. The principles informing this decision (and our application for the interviews in this process evaluation) relate to the aim of the study, sample specificity, use of established theory, quality of the data, and the analysis strategy.

Data collection

- Survey: Study specific self-reported questionnaires will be developed that collect data during both the pre and post switch over period. Questions will assess any changes to clinical pathway, staff mix, or expertise required, surgeon ergonomics, visualisation. Questions will also ask sites to consider challenges and solutions to RAS adoption pre-switchover, and, opportunities and failures post-switchover. These questions will be supplemented with a REINFORCE specific version of the Normalisation MeAsurement Development (NoMAD) tool will be applied within the survey to assess implementation processes at sites for RAS. NoMAD is a self-report instrument based on the four core 'work' constructs of NPT, namely: coherence (sense-making); cognitive participation (relational work); collective action (operational work); and reflexive monitoring (appraisal work).
  Questionnaires will be piloted with REINFORCE co-applicants in advance of dissemination and refined accordingly. The questionnaires will be delivered online and will capture high-level data

on perceived challenges and solutions pre-switchover and realised opportunities and failures post-switchover.

- Interviews: Interview topic guides will also be informed by the four core constructs of NPT. The balance and focus of questions across these four core concepts will be informed by findings from previous work namely Randell et al (16) and REINFORCE -WP1 (namely overall findings of barriers and facilitators used as prompts). The interviews will focus on the main challenges and opportunities for the service implementation pre and post switchover to RAS, with a particular focus on how teamwork and communication influence this process at the team level and also on impacts on service provision, clinical pathways and training at the service level (16). We will also explore procedural details over the switchover (transition) period. Data will be collected from site staff on previous surgeon RAS experience, team expertise, skill mix and training, case mix to assess any impact of learning and speed on roll-out. Interviews will be conducted vis MS Teams or telephone and will be audio-recorded and transcribed verbatim with identifiable information redacted.

An overview of the data collection processes for the process evaluation are provided in Table 2.

11.1. Withdrawal of Participants

During the course of the study participants may choose to stop treatment as per normal clinical pathway but may also choose to stop completing study questionnaires.

Participants may also withdraw their consent, meaning that they wish to withdraw from the study completely. In the case of withdrawal from active follow up other options remain. These options elected for use in the study are covered in the participant information sheet.

According to the design of the study, participants may have the following three options for withdrawal:

1) Participants may withdraw from active follow-up (dedicated questionnaire) and further communication but allow the study team to continue to access their medical records and any relevant hospital data that is recorded as part of routine standard of care; i.e., complications, readmissions etc.

2) Participants can withdraw from the study but permit data obtained up until the point of withdrawal to be retained for use in the study analysis. No further data would be collected after withdrawal.

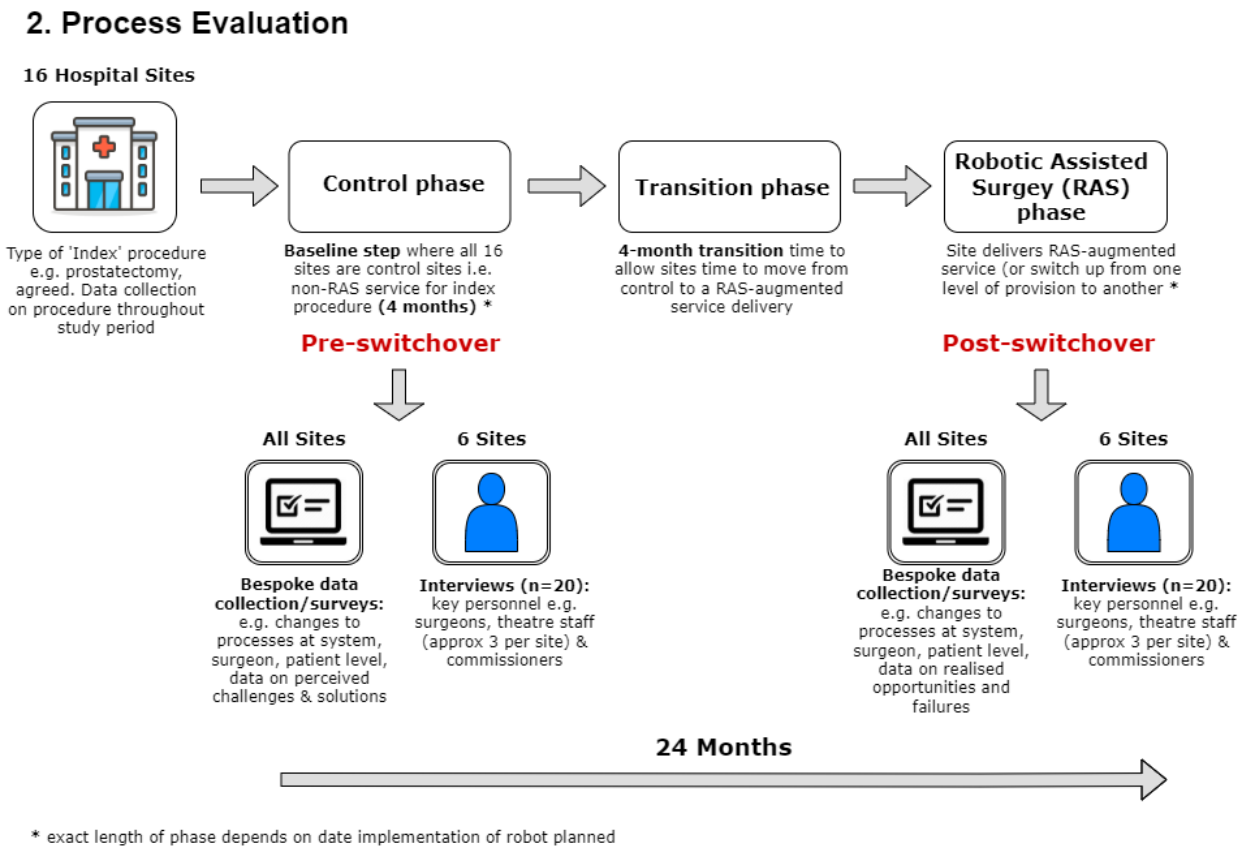
3) Participants can withdraw completely from the study and withdraw the data collected up until the point of withdrawal. The data already collected would not be used in the final study analysis.

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

Table 2. Data collected for Process Evaluation

Aspect of process evaluation	**Data collection method**	**Data collected and data type**	**Purpose**
Pre-switch over	A. Online questionnaire – all sites B. Interviews – 6 sites	A. Free text responses to 2 questions: (a) what challenges do you perceive in relation to adoption of X at your site? And (b) what are the potential solutions you or your site could put in place to overcome these challenges? B. Interviews with key staff in the 6 case sites.	Assess plans for implementation and adoption
Transition	B. Interviews – 6 sites	B. Capture of changes to clinical pathways, staff mix, casemix, and patient management.	Assess immediate impact of introduction of intervention
Post-switch over	A. Online exit questionnaire – all sites B. Interviews– 6 sites	A. Capture of procedural data: previous surgeon RAS experience; team expertise, casemix. A. Free-text responses to 2 reflective questions: If you were to be involved in implementing RAS locally again, (a) what would you continue doing? And (b) what would you do differently? B. Interviews with key staff in the 6 ethnographic sites.	Assess impact of learning (new and existing) and speed of roll-out and adoption.

Figure 2. Data collection for Process evaluation



11.2. Definition of End of Study

The end of study is defined as the point the final participant reaches their 3-month follow-up time point, and all the study data from participants and sites has been entered and queries resolved.

12. STATISTICAL AND HEALTH ECONOMICS ANALYSIS

12.1. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here - details will be fully described in a statistical analysis plan (SAP), the first draft of the SAP will be available after the first TSC meeting. The SAP will be finalised before the final analysis takes place.

12.2. Description of the Statistical Methods

Our primary analysis will be a multi-level mixed effect regression (linear for continuous outcomes) controlling for baseline patient- level covariates. The initial model will be a standard Hussey and Hughes

approach with a random effect for site and fixed effect for time. This approach assumes a common secular trend across sites and a single fixed effect for treatment (assumed constant over time and site). If this proves unlikely, given the potential for differing specialties and index procedures, assumptions will be relaxed using the methods outlined by Hemming et al, allowing treatment/secular trends to vary by site (26). We plan exploratory subgroup analyses comparing sites who are introducing a RAS enabled service to sites scaling up RAS services. We expect missing data to be kept to a minimum but will explore any impact on findings by including sensitivity analysis based on multiple imputation and pattern mixture models. As outlined above, this real-world design is complex and has several well considered assumptions. Contingency has been included should the intended pattern of roll-out not occur according to plan (such as an unexpectedly significant number of sites needing to convert at times outside the design). In such case we have pre-planned for an analysis to treat sites as multiple interrupted time series (27), each site analysed individually and pooled using standard methods for the meta-analyses of interrupted times series studies. The full details of the planned primary analyses will be detailed in the SAP.

12.3. Sample Size Determination

We propose an incomplete stepped-wedge evaluation with 16 sites over 24 months this is practically constrained by the number of sites available and the proposed duration. Each step will last 4 months, the incomplete design includes a 4-month transition to allow sites time to move from control to a RAS-augmented service, and a baseline step where all 16 are control sites. This leaves 4 four-month steps where some sites will be in the intervention arm and some in the control arm. At each step four sites will change. We have conservatively assumed that each site will have 8 eligible procedures a month, (32 in each four-month step), giving an available sample size of 2,560 procedures. Assuming an intra-cluster correlation coefficient of 0.01 (appropriate for continuous measures of patient outcome)(28), we will have just over 90% power to detect 0.3 standard deviations (SDs) and just over 80% power to detect 0.25 SDs difference between arms. Eight procedures a month equates to an average of 2 procedures per week per site. Data on the numbers of patients undergoing likely index procedures suggests that this sample size is fully feasible. For example, the British Association of Urological Surgeons audit data suggests that there are over 7,000 radical prostatectomies undertaken each year in England (29). Similarly a 0.3 SD change represents a “small”-“moderate” change in outcomes (30) – this size of change has been found to be clinically important across a number of settings.

12.4. Missing Data

The primary analysis will be complete cases analysis because we do not anticipate missing data occurring given the procedures that participants are receiving. Sensitivity analyses will test the robustness of estimates to missing data using pattern mixture models.

12.5. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any analysis that is not listed in the final agree SAP will be labelled as post-hoc in all reports.

12.6. Health Economics Analysis

The economic evaluation will comprise a within study analysis; a system level model of implementation or expansion of use of RAS services at scale, and a budget impact analysis. The purpose of the economic evaluation will not be to derive a single estimate of cost-effectiveness but rather to show how cost-effectiveness might vary according to the context in which surgery is provided (e.g., whether the centre is introducing RAS or extending its use, procurement arrangements, size of centre etc.).

Details of the economic analysis are summarised here with details but will be fully described in a health economics analysis plan. This will be finalised before takes place and will be developed to be consistent with the SAP.

Within study analysis: This will compare the costs and outcomes of introducing/extending RAS within a service versus a standard surgical service. The perspective adopted will be the NHS. The planned within study analysis assumes that the sites will be allocated as per the planned stepped wedge design (27). Should this assumption not hold then as described in Section 12.2, each site will be analysed individually and pooled using standard methods for the meta-analyses of interrupted times series studies. In this case costs and quality adjusted life years (QALY) will be analysed as multiple interrupted times series but a within study cost-utility analysis will not be conducted and rather the focus will be on parameterising the economic evaluation model described below.

Estimation of surgical interventions costs

We expect a range of cost scenarios to be developed to reflect whether RAS is being introduced or its use is extended and the different ways in which equipment may be procured (and managed over time). These will range from standard purchasing approaches used in existing economic evaluation models (9) to approaches that more fully explore the real-world complexity; for example, where the equipment is leased or where the equipment is provided by a third party or through charitable donation. These cost scenarios will not present a single cost per patient but rather they reflect the capital cost profile over the time horizon. As such they will reflect multiple interrelated features including: whether this is new

capital or the extended use of existing capital, whether the costs are irreversible or not (based on prior experience we expect the same equipment could be considered as both irreversible or reversible costs depending upon contractual obligations, whereas other costs such as building/structural changes will be entirely irreversible), speed of implementation (informed by the work described above – see Section 11 Implementation of RAS at sites) and capacity constraints. We will also draw out differences in ongoing running costs (e.g., for maintenance and servicing). These costs may be subsumed as part of the equipment costs or may an additional ongoing cost. We expect that these 'running' costs will not be independent of the procurement costs. The scenarios will be developed based on a survey of UK surgical centres, advice from manufacturers and members of the study team. Other intervention costs (e.g., labour, consumables and other items of surgical equipment) will be derived from the study centres using a micro-costing methodology where we itemise each piece of resource use and cost using standard sources (e.g., NHS salary scales, etc.).

Estimation of costs during follow-up period

These will be estimated from responses to a participant questionnaire that will be administered at baseline and 3 months which will elicit use of primary and secondary care services. These data will be combined with unit cost data from routine sources (31, 32). For each scenario considered we will estimate a cost per study participant and a mean cost under a non-RAS enabled, and under a RAS-enabled service model, the analysis for this will be consistent with the main and sub-group analyses described above (see Statistical analysis).

Estimation of quality adjusted life years

Outcomes will be measured in terms of quality adjusted life years (QALY) based on EQ-5D-5L collected at 3 months for each participant. EQ-5D-5L responses will be cross-walked into EQ-5D-3L (33) scores (or scored using an appropriate EQ-5D-5L value set should one become available) and converted into QALYs using the area under the curve approach (34). Mean QALYs will be estimated. As with costs the analyses be consistent with the Statistical analysis.

Estimation of cost-effectiveness

An appropriate regression model (for example general linear model) will be fitted to estimate marginal costs and QALY gains whilst controlling for baseline covariates (e.g., age, sex, EQ-5D utility score) clustered by site (consistent with the Statistical analysis described above (26) where appropriate). The precise nature of the regression model will depend on the data collected from the trial. The results will be expressed in the form of incremental costs, incremental QALYs and incremental cost-per-QALY for

each scenario considered. Scenarios will vary according to the procurement costs, characteristics of the surgical centre (e.g., size).

Stochastic and deterministic sensitivity analysis (DSA) (35) will also be used to investigate effects of uncertainty/assumptions in the regression model parameters and heterogeneity in the patient population. In the DSA, each parameter will be set to extreme but plausible value to assess the changes in the cost and QALYs. Stochastic sensitivity analysis will utilise the non-parametric bootstrapping technique (36) with multiple bootstraps (e.g., 1000), to explore the impact of statistical imprecision surrounding the point estimates of costs, QALYs and cost-effectiveness for each scenario. Cost-effectiveness acceptability curves (CEAC) (37), cost-effectiveness (CE) plane (scatter plot) and tornado diagram (for DSA) will be used to illustrate these uncertainties in the cost-effectiveness.

Exploration of cost-effectiveness and budget impact to the NHS of the introduction of RAS at scale.

Modelling approach

A systems model (likely a Discrete Event Simulation (38)) will be developed to explore the impact of changing the scale of RAS at the level of a service provider (e.g., an NHS Acute Care Trust). Its purpose is to explore the impacts of different ways RAS might be implemented in practice and what effects changing the scale of its use within a provider will have. For example, for a situation where RAS is introduced, we will explore how its use might change over time and draw comparisons with the situation where RAS is not introduced. We will do this modelling the costs and outcomes for individual patients who are treated in that provider with the target conditions over a 10-year period (the likely maximum lifespan of RAS equipment). As the impacts of surgery at for an individual may be lifelong the costs and outcomes for each patient will be modelled over their lifetime with what happens to a patient over time depending upon which type of surgery they receive and their individual characteristics (age, sex, comorbidities, etc.).

The model will predict the system level performance and explore how this might change as the context of the service changes. It will do this from the perspective of the NHS.

Parameterising the model

A set of parameters [transition probabilities and state rewards (cost and health utility scores)] will be assigned for each patient based on patient characteristics in each scenario modelled. These parameters to populate the model will come from the study, routine data sources (e.g., Hospital Episode Statistics) and published literature.

Transition probabilities: The transition probabilities of patients between states in the model will be derived from the study data, existing health technology assessments and economic evaluations supplemented by evidence from intervention reviews relevant to each index procedure considered. Data will be extracted on the incidence of key events (e.g., complications and re-intervention rates), and progression of disease (which will also help in the refinement of model states). This approach is adopted as there have already been numerous comparisons of these surgical techniques and these secondary data will be utilised to allow the focus of research efforts on the system level impacts rather than duplicating existing research.

Resource utilisation and costs: Broadly, each scenario modelled will consider the impact in terms of human resources (staff and training), consumables, infrastructure (capital costs), post-operative care (e.g., length of stay in the hospital and outpatient care (including the utilisation of primary care services). The intervention costs will be based upon the cost scenarios described above for the within trial analysis. Use of subsequent services for the short-term will come from the trial. Later costs will be derived from existing health technology assessments and their attendant economic evaluations on the use of robotic surgery compared with laparoscopic and open surgery (9).

Health state utilities: In order to estimate impacts on individuals' quality of life in each of the scenarios modelled health state utilities will be assigned to each state of health a patient may find themselves in over their estimated lifetime. These data will be sourced from the trial. existing health technology assessments, specialist data bases (e.g., https://cevr.tuftsmedicalcenter.org/databases/cea-registry) and a review of published literature.

Assessment of cost-effectiveness: The results will be presented as a set of cost-consequence analyses (CCA) (one for each scenario modelled) as a balance sheet. This approach will be adopted in order to present the wider system effects not readily monetarised or incorporated into QALYs. In the CCA, the consequences considered will map onto those developed for the trial (see Outcomes) we will also explore with stakeholders if there are other considerations that are not directly captured by our study outcomes. These might be consequences to other group (carers, family members and other social networks) and to the service i.e., spillover effects. We will draw upon advice from our PPI representatives and other stakeholders to determine if there are any spillover effects that should be at least mentioned in the CCA even if they cannot be quantified.

A cost-utility analysis (CUA) will also be conducted with results presented as incremental cost, incremental QALYs, incremental cost per QALY (difference in total costs divided by difference in total QALYs) for each of the scenarios modelled compared to the counter factual service (e.g., RAS was not introduced or the use of RAS was not extended).

For both the CCA and CUA, uncertainties in model parameters will be explored in deterministic and probabilistic sensitivity analyses (PSA). Deterministic analysis will consider the impact of different discount rates, different time horizons and different parameter sets (e.g., different assumptions about what type of surgery is used should further surgery be required). In the PSA, suitable distributions (35, 39) will be assigned to each model parameter (the choice of these distributions will be guided by parameter type and standard statistical methods of their estimation but for example, gamma or log normal distributions for cost parameters, beta distribution for utility and transition probability parameters are commonly used) and Monte-Carlo simulation (which samples the parameters at random) will be performed to generate the estimates of costs and outcomes accounting for any parameter uncertainties. Similar to the approach described above CEACs, CE planes and tornado diagrams will be used to illustrate the effect of parameter uncertainties in the model.

Budget impact analysis: A simplified version of the system model will be developed to estimate the budget impact to an NHS provider of introducing/extending RAS. A budget impact is a forecast of the financial consequences of the decision to invest in the introduction or expansion of RAS services. The annual total costs to the NHS over 10 years will be estimated. An illustrative set of scenarios developed in collaboration with the study team and stakeholders will be presented but the model will be constructed so that a range of scenarios and different parameter values can be explored by a user.

12.7. Process Evaluation Analysis

Data analysis

- Survey: Questionnaire data will be presented using narrative summaries to describe the findings. We will analyse the data at an aggregate level, but also present findings based on stage of implementation.
- Interviews: Interview analysis will begin during data collection, with initial analysis or preliminary interviews being used to inform subsequent data collection. This process allows for development and refinement of key topics for exploration throughout the interviews. Transcript will be imported into NVivo to aid with analysis. Interview data will be coded deductively with themes informed by the NPT. However, we will also include a parallel inductive analysis to capture any data that doesn't align with the NPT themes. These deductive and inductive themes will be developed into a thematic framework which will be systematically applied to all interview transcripts. Interview data will be coded and compared through a process of constant comparison [21] to provide a summary of the key points about what stakeholders consider

important in this context. The coding will be led by one member of the research team with the codes and associated data reviewed by a second member of the project team.

- Mixed methods analysis: The quantitative and qualitative data described above will first be analysed separately. During data analysis, the data will then be mixed for the 6 case study sites included in the interview study using data triangulation to provide a more detailed understanding of the site specific contextual issues associated with implementation (40). The methodological approach of triangulation gives equal weighting to both data sets when addressing the objectives of the process evaluation. The data will be compared across cases to explore where there is agreement or dissonance and where findings or outcomes emerge in one data set but aren't confirmed by another. This approach will utilise a matrix approach to map out the findings and provide a synthesis from across the various datasets. It will be used to explain and inform the integration of findings.

Integration of findings

The process evaluation will be analysed in advance of knowing the main REINFORCE trial results, and the analyses of each will initially be independent of one another. On completion of both trial and process evaluation analyses, the results will be considered with regard to the development of hypotheses regarding potential implementation in one context compared to another and how and why RAS was delivered successfully in some settings and not in others. The data from the process evaluation may potentially be used to explain the outcomes from the trial with regard clinical effectiveness. This may provide justification for additional analyses based on the trial outcome and process evaluation data to explore and understand why RAS worked (or not) in various contexts.

13. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

13.1. Access to Data

Direct access will be granted to authorised representatives from the University and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

13.2. Data Recording and Record Keeping

Clinical data will be entered into the database by the designated team members working in each recruitment site, together with data from any patient questionnaires completed at clinic. Patient completed questionnaires returned by post to the central study office will be entered by the central study team. Staff in the central study office will work closely with local team members to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

All paper documents will be stored safely in confidential conditions (i.e., locked cabinets) both at local hospital sites and the central study office. Other than the signed consent and Patient Details form, the participant will be referred to by the study participant number/code, not by name on all study-specific documents entered in the study database.

14. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

14.1. Study monitoring

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study. Regular monitoring will be performed according to the study specific Monitoring Plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents as these are defined in the study specific Monitoring Plan. Following written standard operating procedures, the monitors will verify that the clinical study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

14.2. Study Committees

The study will be supervised by the Project Management Group (PMG) comprising grant holders and representatives from the SITU and CHaRT Trial Office. The PMG will meet at least monthly within the first and last six months of the trial and every two months in between.
The Trial Steering Committee will be set up and run in accordance to their Charter. All members will have to sign to agree to the conditions of the Charter before sitting on a committee.

15. PROTOCOL DEVIATIONS

A study related deviation is a departure from:

- other study document or process (e.g., consent process)
- Good Clinical Practice (GCP) or any applicable regulatory requirements.

Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Approvals

Plans for the evaluation of the multi-centre stepped-wedge evaluation (with integrated process evaluation and economic assessment) of the introduction and scale-up of RAS services in the NHS have been independently reviewed by the University of Oxford Research Governance, Ethics & Assurance Team. Following review, they directed that this project falls under the remit of service evaluation, as per "Defining Research" guidance from the NHS Health Research Authority. As such, the service evaluation will be registered locally each local Clinical Audit Team/Clinical Effectiveness Team/Clinical Director, as appropriate.

The Investigator will submit and, where necessary, obtain approval from the above parties for conduct of the study.

16.2. Ethical Considerations

No study-specific ethical issues are anticipated. The study follows routine care implemented at a participating Trust and follows the routine patient pathway for the identified index procedure being evaluated at that site. The study involves no additional risks to participants beyond those of routine standard care. Participants will be informed of the standard risks associated with the surgical procedure.

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with the principles of the Declaration of Helsinki and Good Clinical Practice.

16.3. Transparency

Prior to the collection of data from the first participant, the study will have been registered on a publicly accessible database. The study information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the study.

16.4. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.5. Expenses and Benefits

No payments or other benefits to patients will be made. There are no study specific follow-up visits or procedures in addition to normal care.

17. FINANCE AND INSURANCE

17.1. Funding

The study is funded by the National Institute of Health Research, Health Research Health Services and Delivery Research (HS&DR) Programme (NIHR131537). The Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences at the University of Oxford will manage the finances and budget in collaboration with the University of Aberdeen and Newcastle.

17.2. Insurance

The University of Oxford has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the study (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by NIHR Health Research Health Services and Delivery Research (HS&DR) Programme. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. ARCHIVING

The Trial Master File (TMF) including all essential documents must be retained for at least 5 years after the completion of study-related activities. The TMF will be archived centrally, and the Investigator Site Files will be archived at site.

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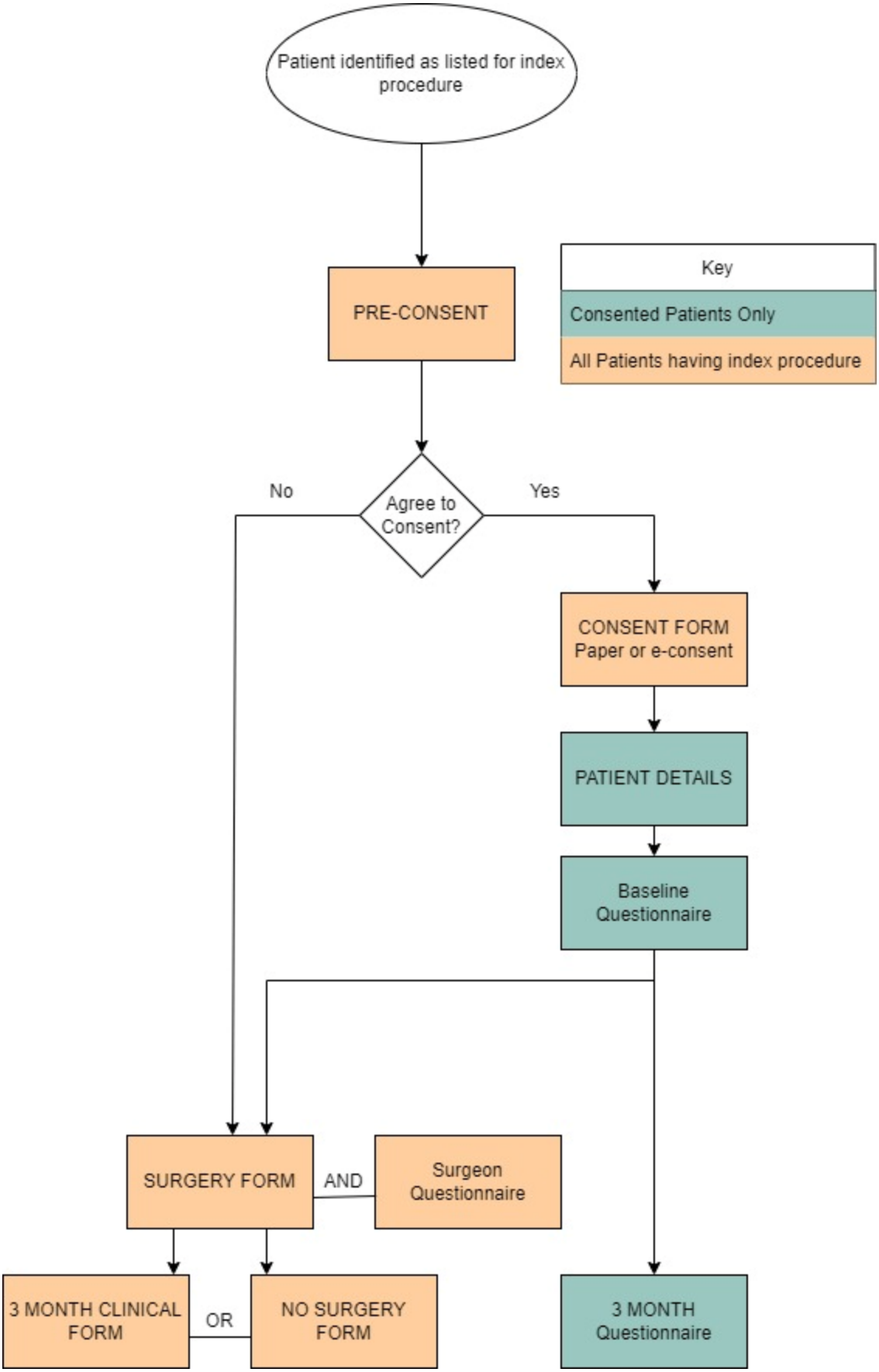
21. APPENDIX A: DATA COLLECTION FLOW CHART



22. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.