# Near Infrared Fluorescence (NIRF) Imaging to prevent Post-surgical Hypoparathyroidism (PoSH) after Thyroid Surgery (NIFTy) – preparatory qualitative work prior to a phase II/III pragmatic, multicentre randomised controlled trial

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REVISIONS

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# Contents

# 1. SUMMARY

**Study Title: Near Infrared Fluorescence (NIRF) Imaging to prevent Post-surgical Hypoparathyroidism (PoSH) after Thyroid Surgery (NIFTy) – Preparatory qualitative work for a phase II/III pragmatic, multicentre randomised controlled trial**

**Study Short title: NIFTy Observational study**

## 1.1 Background:

Parathyroid glands are tiny glands in the neck behind the thyroid gland that control the level of calcium in the blood. More than 12,000 patients undergo thyroid surgery every year in England alone, and a common problem is damage to or accidental removal of parathyroid glands. This causes a condition called hypoparathyroidism; this may be a temporary condition, but in up to 12% of cases, it is long-term requiring lifelong medication and care. It reduces blood parathyroid hormone and calcium levels resulting in a wide range of symptoms (such as tingling & numbness in the extremities, nausea and nocturnal cramps), longer hospital stays and requirement for frequent blood tests to monitor calcium levels & ongoing treatment. It has a significant impact on patients' quality of life and the potential for kidney damage, accumulation of calcium in the tissues and seizures; this can be life threatening.

A new technology called 'fluorescent imaging' (near infrared fluorescence – NIRF) may facilitate the identification and preservation of parathyroid glands during thyroid surgery. The aim of the trial (for which a separate ethical approval application will be made) will be to find out how many patients develop short and long term parathyroid damage following the use of this technology compared to those who underwent surgery in the standard manner. The study will also determine if this new treatment will reduce hospital stay after surgery and improve quality of life for patients.

The Medical Research Council guidance on the development of complex interventions states that the intervention should 'consistently provide as close to the same intervention as possible' by 'standardising the content and delivery of the intervention'. However, we need to balance being able to describe the intervention in sufficient detail that other surgeons can replicate it, and standardising to the extent it is inflexible for surgeons and no longer reflects real world practice. Therefore, a balance between standardisation, and flexibility is needed.

Qualitative research methods allow for the identification of the key components of a complex intervention, such as surgery, within their original setting. The present study will take place prior to the RCT and will inform the development of the surgical protocol, develop a tool for collecting data about how fluorescent imaging affects treatment related decision making (i.e. how does it affect the intraoperative decision relating to dissection of the thyroid and whether to autotransplant the parathyroid glands?).

## 1.2 Study Objectives (for this ethical approval application)

In the NHS, fluorescent imaging (NIRF) is not used in regular practice in the UK, so this work will develop and agree the protocol for the intra-operative steps that surgeons in the trial will use. To achieve this, we will:

- Observe and video-record surgeries to identify and describe key components of total or completion (where a previous surgery has removed part of the thyroid and this operation will remove the remaining portion) thyroidectomy, with or without central neck dissection.

- Use the data collected to identify and agree timing and use of NIRF for the planned trial.
- Establish which intervention components should be a) mandatory b) optional, and work with surgeons to agree the protocol for the operative steps.
- Develop and pilot a data collection tool for assessing intra-operative decision making.

## 1.3 Patient Population:

Adult patients due to undergo total or completion thyroidectomy with or without central neck dissection. Indications for surgery may include Graves' disease, suspected or confirmed thyroid cancer and goitre causing compressive effects.

## 1.4 Design:

Video-recording of up to 15 thyroidectomies, non-participant observation of surgeries; interviews with surgeons post-surgery; survey of participating surgeons; expert clinical panel to agree protocol for surgery in main trial.

## 1.5 Output:

Protocol to take forward to NIFTy randomised clinical trial; data collection sheet to record intra-operative decision making (related to the use of fluorescence).

## 2 Background

Post-surgical hypoparathyroidism (PoSH) occurs as a complication of a number of different procedures. The vast majority (78-91%) of patients in the community with hypoparathyroidism have PoSH; i.e. this is primarily an iatrogenic disease [1]. Thyroidectomy is the commonest predisposing operation and is performed for a range of benign & malignant conditions (e.g. multinodular goitre, hyperthyroidism, thyroid cancer). The mechanisms of PoSH include devascularisation, direct damage and inadvertent removal of the parathyroid glands [2]. Reliable preventative measures have not been developed. Many techniques have been explored e.g. different surgical approaches, extent of surgery, perioperative medications, routine parathyroid auto-transplantation, high ligation of inferior thyroid artery, use of loupes and haemostatic measures. The effectiveness of these measures were recently summarised in a review [3] which shows that although temporary hypocalcaemia rates may be reduced by some interventions, their impact on long-term PoSH is minimal.

In the short term, PoSH can lead to troublesome symptoms including tingling, numbness of the extremities and oral cavity, cramps and nausea. Its occurrence can prolong hospital stay [4] and is associated with multiple hospital attendances, readmission to hospital [5] ongoing monitoring and treatment – all significantly increasing costs of treatment. In the long term, post-surgical hypoparathyroidism can cause a wide range of symptoms, a 'high burden of illness' [6] and a negative impact on all aspects of quality of life [7] . Over 12,000 thyroid operations are done annually in England alone; a significant proportion of which involves bilateral thyroid surgery and carries a risk of this complication. A significant reduction in the incidence of hypoparathyroidism has potential to significantly reduce morbidity and costs associated with monitoring and treatment.

Recent studies have demonstrated the feasibility of near-infrared fluorescence (NIRF) as an intraoperative tool for anatomical guidance [8, 9] and for cancer surgery [10, 11]. The potential of NIRF in parathyroid (PT) identification and preservation has been demonstrated in animal models [11] and a recently completed phase I human trial [12]. Although parathyroids auto fluoresce naturally, adding a fluorescing dye means the fluorescence can be observed more clearly, and using dye has the potential to determine viability of the PT glands in addition to identifying the glands. This will enable surgeons to decide on the need for autotransplantation of the PT glands during surgery. These claims will be tested in a future study.

The Medical Research Council guidance on the development of complex interventions states that the intervention should 'consistently provide as close to the same intervention as possible' by 'standardising the content and delivery of the intervention' [13]. The SPIRIT statement [14] provides a checklist of 33 items to be reported in trial protocols, including items relating to the 'intervention' and the TIDieR guidance [15] – an extension of item 11 of SPIRIT – comprises 12 items relating to the description of all types of intervention, and recommends that the duration, dose and materials used in the intervention are provided. However, these documents are not easily applicable to surgical interventions.

Different surgeons could deliver the same treatment in different ways, so we need to be able to describe the intervention in the clinical trial protocol to allow delivery and fidelity to be accurately assessed [16]. The level of detail needed depends on the nature of the research question and study design [17, 18]. As we plan a phase II/III randomised controlled trial to test the efficacy of near infra-red fluorescence (NIRF) imaging, the protocol needs to be more tightly defined than for later trials.

To address the limitations of the SPIRIT [14] and TIDieR [15] guidance, an approach developed by Blazeby and colleagues will be used in this study to allow us to clearly describe the intervention and how it should be delivered [19]. Their typology provides a framework for use during trial design to standardize the delivery of surgical interventions and document these details within our protocol. Specifically, it advises that the key components of the surgery are mapped and decisions are made about whether, and to what extent, the different components/steps need to be standardised. Finally, the typology then provides a framework for monitoring agreed intervention standards during the trial and determining fidelity. This study will undertake the work required to produce an agreed protocol for the way the surgery should be undertaken and how and when the NIFR technology will be used in the trial.

Qualitative research methods allow for the identification of the key components of a complex intervention, such as surgery, within their original setting. The present study uses a methodology developed and used successfully by Donovan and colleagues in Bristol in a study of gastric band surgery [16]. The present study uses their approach to develop an acceptable, and replicable protocol for use in the later NIFTy randomised controlled trial.

The current ethical approval request relates to work which must be undertaken prior to the trial to inform the methods for collecting data in the main study. Specifically, we need to develop a tool to collect data on how fluorescent imaging affects treatment related decision. To achieve this goal, this study will map what happens during surgery now, and determine how best to collect data on the intra-operative decisions the surgeons in the future trial will make.

## 2.1 Future work

A phase II/III randomised controlled trial has been funded by the National Institute for Health Research (NIHR EME programme Ref 17 11 27). The trial is currently in set-up (separate ethics application planned). The trial will test the efficacy and effectiveness of NIRF imaging technology.

### 2.1.1 The focus of the present study

In line with good practice, prior to the trial opening we need to gain consensus from the participating surgeons about the specific points during the surgical procedure where the technology can be used and agree the level of intra-operative standardisation for the trial [13, 15]. This is essential because if surgeons differ significantly in their surgical approach we will be less confident that any differences in patient outcomes are due to being able to visualise the parathyroid clearly during surgery, or due to differences in surgical technique.

The data obtained in the current study will be presented to a formal expert consensus meeting where participating surgeons will agree how the NIRF technology will be used in the trial intervention arm. It will also provide data about possible moderators and mediators of the effect of NIRF technology, which will be explored in the statistical analysis. Fluorescent imaging is not used routinely in thyroid surgery in the UK, but NIRF has been used in research studies to aid real-time intra-operative visualisation of tissue and to differentiate between tissue types. NIRF can be used early during thyroid mobilisation to identify where glands are to enable preservation of normal glands during thyroidectomy or at completion of lobectomy to assess viability of the parathyroid (i.e. is it vascularised) and to make a decision for auto-transplantation of the parathyroid, if appropriate.

The key output from the qualitative work will be a consensus document and agreed protocol, with good clinical buy-in, for the intra-operative steps and the use of NIRF imaging during surgery.

The qualitative research will also provide information about how to best record the treatment related decisions that surgeons make which will inform the data collection and plan for auxiliary causal inference analyses in the planned randomised controlled trial.

We will also develop a manual and short videos describing the timing of the intervention during thyroid surgery, explaining the use of the software, what to look for in the operating field and how to make decisions on fluorescence imaging.

# 3 Aims and objectives

This study aim is to develop a working surgical protocol for use in the future NIFTy randomised controlled trial. The study objectives are:

1. To collect video and audio data on up to 15 surgeries detailing the surgical procedure to identify the intervention components and steps.
2. To iteratively design and test out a surgical decision recording tool for use in the trial.
3. To observe the same surgeries to collect data on clinical and contextual factors that may influence the decision around the use of the imaging technology during surgery to inform development of the data collection tool.
4. To interview operating surgeons to gain an understanding of how the surgery went (usual/unusual steps), imaging and surgical decisions that were made, and why.
5. To undertake a survey of participating surgeons to gain their thoughts on the intervention components and steps and which should be mandatory/optional for the trial.
6. To undertake an Expert Panel Consensus meeting to agree the final surgical protocol.

## 3.1 In-depth exploration of intervention within the operating theatre

## 3.2 Design

A case study approach will be used [16, 20, 21] to observe and understand 'usual practice' and how surgeons choose to use the NIRF imaging technology intra-operatively. This work will address objectives 1-4 above.

### 3.2.1 Eligibility

Patient inclusion criteria:

Adults, 18 years or older

Able to provide written informed consent

Adult patients due to undergo total or completion thyroidectomy with or without central neck dissection (indications for surgery may include Graves' disease, suspected or confirmed thyroid cancer and goitre with compressive effects)

ASA </= 3

Able and willing to comply with the terms of the protocol

Exclusion Criteria:

Not able to give written informed consent.

History of intolerance or sensitivity to ICG (the dye to be used)

Patients with significant renal impairment (defined as eGFR <40 ml/min/1.73m$^2$)

Patients undergoing concurrent parathyroid resections

Known allergy to ICG, iodine, iodine dyes, or drugs known to interact with ICG e.g. anticonvulsants, bisulphite containing drugs, methadone, nitrofurantoin.

Patients who are pregnant or breast feeding

### 3.2.2 Sites

The study will take place in up to 3 teaching hospitals who have all confirmed they have capacity to provide data for case studies (Sheffield, Leeds and Hull).

### 3.2.3 The Intervention

This study will use the FluobeamLX machine to provide NIRF. The FluobeamLX is CE marked for thyroid and para-thyroid surgery and allows the parathyroid glands inside the central compartment of the neck to be made visible, both with and without ICG (a short-acting dye). The imaging technology is not currently used in the NHS. The NIRF technology comprises fluorescent imaging device that is attached to a computer to take video and still images of the inside the patient's neck. The camera contains a class 1 laser with white light emitting diodes and a charge-coupled device camera. A control box is linked to a laptop where real time still and video images are displayed on screen and recorded. To enhance the fluorescence, a short acting dye (ICG) is injected through a vein, from where, if the glands are viable the dye will be drawn to the parathyroid glands and will aid visualisation.

### 3.2.4 Procedure

Clinicians will be advised to conduct the operation as they usually would and the use of the imaging technology will be completely at the surgeons' discretion (including any decision not to use it). With patient consent, ICG may be administered (injected into a vein) at key points during their operation (up to a maximum of six doses). When the surgeon is about to use NIFR, the researcher will ask the surgeon (before they administer the ICG) to state why they have chosen to use the technology at that point, and what the next step in the procedure will be. This information will be recorded and used to design the decision recording tool that we will use in the future trial. The imaging technology (NIRF + ICG) will then be used. The research team will not influence the surgical procedure, but will observe the procedural components and steps, including how and when NIRF is used.

Following the surgery, a discussion will take place with the surgeon (see section 3.2.10) about the added information (if any) the NIRF provided, where and when they found the dye to be helpful/not helpful. This study is purely observational and does not intend to change practice but will map when NIRF may be useful intra-operatively by different surgeons and to identify decision outcomes to develop a decision recording tool for use in the trial.

### 3.2.5 Recruitment process

Patients will be identified by the surgical centre over an 8 week period from current surgical lists. Patients fulfilling the entry criteria will be approached by the clinical team to discuss the study. Patients will receive an information sheet at their surgical pre-operative meeting. This meeting is usually several weeks before the surgery, and the study will be explained to patients. Potential participants will have at least 48 hours to consider participation in the study. Verbal consent to the study will be gained by the clinical team by telephone as the video recording equipment will need to

be set up prior to the surgery. The right of the patient to refuse consent without giving a reason will be respected.

Patients who have previously given their verbal consent will be invited to give their written informed consent on the day of their surgery, including explicit consent to transfer a copy of their signed consent form and data to the research team.

### 3.2.6 Sampling strategy

Completion and total thyroidectomies at each centre will be purposively sampled as cases for study. Diversity in terms of procedure (total vs completion thyroidectomy) and with or without central neck dissection will be sampled. A sample of 4-6 surgeries from each site will be sought.

### 3.2.7 Video recording and observation of operations

Video recording of up to 15 purposively sampled surgeries will be undertaken with patient and surgical staff consent.

Digital video recordings of operations will be undertaken by the hospital medical education teams, using standard techniques. This involves the use of a fixed camera that focusses on the operation field (i.e. neck area only), and may include the use of a hand held camera to collect close-up images. The actual technology used will vary depending on availability at each site, and the operating theatre used on the day. Still and video images from the fluorescent imaging device will also be collected to demonstrate the fluorescence. Patient anonymity will be maintained in the video recordings. No patient identifiable features will be visible (e.g. face is covered during surgery) and patients will be identified only by an ID number on the video recording. This number will be unrelated to any patient identifier. Video data will be collected from the point of knife to skin (i.e. after patient identity checks are complete) to the end of the surgery. Data on the clinical presentation, patient age and gender will be collected. Concurrent non-participant observations will take place.

### 3.2.8

### 3.2.9 Non-participant observation in the operating theatre

With patient and staff consent, we will undertake observations of the operations that are being video recorded. This will involve two researchers being present in the operating theatre in a non-participatory role. Using an observation schedule developed for the project (see appendix 1 for the schedule) we will record what happens during the surgery and how this may affect clinical decisions. The aim will be to triangulate the data provided by the video recording, observations and interviews to understand the clinical and contextual factors that influence the decision to fluorescence intra-operatively. Observations will be made by hand onto the observation schedule. Two researchers will be present at all surgeries, one clinical research fellow and one non-clinical (MT). Dual observations will increase the study validity and ensure both clinical and non-clinical interactions will be recorded. Findings from the observations will be explored in interviews with surgeons.

The observation schedule will also record the surgical decisions made. These data will be used to develop a surgical decision recording tool to be used in the phase II/III trial. Development will be an iterative process with input from the surgical teams involved. The decision recording tool will be a brief questionnaire to be used before NIRF is used to capture whether or not the fluorescence has

influenced clinical decision making.

### 3.2.10 Interviews with surgical team members

With their consent, we will interview all operating surgeons immediately after surgery to gain an understanding of how the surgery went (usual/unusual steps), imaging/surgical decisions that were made (and why), and information provided by the imaging. These interviews will last 10-15 minutes and will be audio-recorded, with permission. Semi-structured, follow-up interviews with all surgeons will be undertaken 2-4 weeks later, using a topic guide developed from the existing literature and clinical knowledge. Questions will explore factors that influence the decision to use imaging (e.g. surgical expertise, location of glands, pathology), and timing of its use, as well as their views of using the decision recording tool intra-operatively, the use of the device software, and what they looked for in the surgical field when using the device. The follow-up interviews will take place after the initial analysis of the case study data (video, audio data and notes) has commenced, to enable discussion of similarities and differences between centres and surgeons in terms of how the operation was performed, and when fluorescence was used. Views about standardisation of the operation will be explored. The topic guide will comprise a list of open-ended questions to ensure that all topics were covered in each interview but will be flexible enough to enable issues of importance to emerge (see appendix 3). Emerging findings will be explored in later interviews. Interviews will be audio recorded with permission.

### 3.2.11 Data analysis

Analysis of the case studies (video, audio and field notes) will be undertaken by a medically qualified surgical trainee with no direct clinical experience of fluorescence technology, supervised by an experienced applied health researcher (MT) and a consultant surgeon (SPB). NVivo qualitative data management software will be used to store the audio and video data as well as observational notes on each case. The video and audio recordings of the surgical procedures will be reviewed unedited. This will involve the researcher watching and re-watching the videos to document the actions, instruments and movements visible on screen. The actions visible on the video will be grouped into the components and steps of the operation to generate a clear step-by-step account of the procedure [16]. The accuracy of the analysis will be checked by a consultant surgeon. Relevant clinical discussions will be transcribed from the audio recordings; discussions unrelated to the surgery will be omitted. Notes from the observations will be typed up immediately after the surgery and managed using NVivo. The audio data and observational notes will be synchronised with the video data. This will allow a richer understanding of each step and its purpose. The data will then be compared across sites to explore similarities and differences between surgeons and centres. The iterative nature of the analysis will allow us to elucidate the (un)usual steps and common processes across and between surgeons and centres, as well as the points at which surgeons choose to use NIRF.

The interview data will be used to confirm, challenge and clarify findings from the videos and observations. Any unexpected steps that are identified within the video or observation data, will be explored with the surgeon in the post-operative interview. Post surgery interviews will be transcribed verbatim using an external, professional transcribing company (see GDPR). Framework [22] approach to data analysis will be used to allow themes to be derived from the data. Transcripts will be coded by ascribing words or phrases that capture the meaning of the text to identify common emerging themes. The coding index will be developed and coded material regrouped, as new themes and categories emerge from subsequent interviews. Matrices will be developed to facilitate analysis of the textual data to explore differences and similarities within themes, and relating findings back to the video and observational analyses and across sites.

The output will be a template that identifies the components and steps of the procedure, the ordering of the different components at each site. A qualitative analysis of the surgeon's rationale for their approach will accompany the template.

## 3.3 Wider consultation with surgical community

To ensure we have clinical buy-in for the surgical protocol it is important that we consult with the teams who will take part in the phase II/III trial. To achieve this, we will undertake objectives 5 and 6:

- To undertake a survey of participating surgeons to gain their thoughts on the intervention components and steps and which should be mandatory/optional for the trial;
- To undertake an Expert Panel Consensus meeting to agree the final surgical protocol.

### 3.3.1 Design

Online survey and Expert Panel.

Findings from the initial work described above, including brief anonymised extracts of videos from the surgeries clips are (likely to be 1 to 2 minutes each) will be shared with surgeons who have expressed an interest in recruiting to the trial, via a short web-based survey.

### 3.3.2 Sample

Operating surgeons (consultant and registrars) who have agreed to participate in the phase II/III trial.

### 3.3.3 Method

This will be a closed survey. A link to the survey will be sent by email to the operating surgeons, with an invitation for them to respond, using Qualtrics survey software hosted by the University of York (Hull York Medical School host some software at York University). Data will be downloaded for analysis at the University of Hull. Feedback will be sought from surgeons on the use of NIRF imaging during thyroidectomy, and the type of standardisation that may be needed for each component of the surgery (mandated/optional). Brief anonymised video clips will be used to illustrate the surgical steps and the use of fluorescence (video clips will only be used with patient permission), and structured and open text feedback requested (e.g. step XX should be mandatory/optional – please

explain decision). The final content of the survey cannot be determined until the observational work is complete and an amendment will be submitted to the ethics board for approval.

The results of the survey will be analysed descriptively (e.g. proportion of surgeons agreeing/disagreeing with each statement) and qualitative findings will be analysed thematically using Framework analysis [22] and presented to the Expert panel for discussion.

## 3.4 Expert Consensus Panel

We will hold an Expert consensus panel meeting to consider the evidence collected from the qualitative work and survey to agree the mandatory/optional aspects of the intervention. Using a nominal group approach, 8-10 of the participating surgeons will be invited to take part [23, 24].

Findings from the surgical observational work and clinical survey will be circulated prior to the meeting. Members will be asked to consider and record responses using either post-IT notes or voting software to questions regarding components and steps of the surgery and the timing of fluorescence. All ideas will be discussed and then voted upon to agree the mandatory/optional aspects of the intervention. The group will be co-facilitated by an independent Chair with significant clinical expertise.

## 3.5 Outputs

For the trial, a clear protocol will be developed using the typology constructed in phase 1 which will detail the surgical steps and type of standardisation (mandated, prohibited, optional) and the conditions under which each step is allowed or not, as agreed by the expert panel. In addition, clear instructions about when NIRF +ICG can/should be used will be provided within the protocol.

The bespoke checklist be finalised using the results of the expert consensus meeting to allow the collection of data on the fidelity of intervention delivery; specifically how the key component and steps were carried out, what was and was not delivered and why, following recent guidance set out by Blencowe and colleagues [19].

## 3.6 Ethical and Regulatory considerations

The study will use the FluobeamLX device to identify and illuminate the thyroid and para-thyroid glands. The device is CE marked for this purpose. Phase I study data supports its use in humans [12], and the potential use of auto-fluorescence and the use of dye has been highlighted in the phase I study. NIRF + ICG is not currently used for this purpose in NHS practice.

Patients will be asked to consent to the use of the NIRF + ICG during their surgery, and for their surgery to be video recorded. NIFR and ICG will be available to the surgeon to use, but as this research aims to plot the steps and components of the surgery, the use of the device will be at the surgeons' discretion. We are not planning to affect or change patients' clinical management. Each site will continue with their local protocols for the surgery.

In this observational study, patients will be asked to consent for clinical data to be collected and will be asked to allow a video and audio recording of their surgery to be used for research and training purposes, including for later research. Written consent will also be obtained from patients to allow two researchers who are not part of the clinical team to be in the operating theatre to observe their surgery (as non-participant observers).

Patients will not be able to be identifiable on the video. Patients faces are covered routinely during this procedure and only the neck area will be visible. If a patient has an easily identifiable tattoo this will be pixelated out. Participants will be identified by an ID number on all recordings and data collection tools. This will not be related to their date of birth, name or other personal information.

## 3.7 Data protection and confidentiality

The use and control of all data will comply at all times with the requirements of the General Data Protection Regulation (GDPR 2018). The study will be registered with the local Data Protection Officer at the University of Hull. Further information on how the University of Hull manage data is provided in the University of Hull Data Privacy notice.

All data management procedures will be detailed and referred to as the Data Management Plan. All data will be entered and checked by a second person (either a clinician or researcher, as appropriate).

The Senior academic leading the qualitative work (MT) and Clinical Research Fellow will have honorary contracts at each site and will abide by NHS confidentiality guidelines and requirements.

The University of Hull will be responsible for data collection, recording and quality. Data will comprise video, audio (from surgery and interviews) and observation notes.

Video recordings will be undertaken by local NHS IT/Medical Education teams using NHS equipment. Audio recordings (of the surgery and subsequent staff interviews) will be made with an encrypted digital audio recorder. These data will be transferred immediately to a University of Hull encrypted laptop, saved to folders using an ID number. Audio and video data will be transferred on the encrypted laptop from the research sites to the University of Hull for analysis. Handwritten notes will be taken during the surgery. These will be taken by hand or posted to the University of Hull.

Interview data (audio files) will be transcribed professionally using a company with whom the University of Hull has a GDPR compliant confidentiality agreement. All transcripts will be checked for any identifiable data, and anonymised.

The online survey will be anonymous and administered through the University of York. Access to the data will be managed by the Senior academic (MT) and only available to relevant members of the research team, with aggregate data provided to the Expert panel.

Identifiable data will be stored in the Hull Health Trials Unit (HHTU) Data Safe Haven. Data will be held in accordance with the General Data Protection Regulation (GDPR 2018). The HHTU holds an NHS IG toolkit (replaced by the Data Security and Protection toolkit from March 2019) covering all systems within the HHTU. The study will be conducted in compliance with the current approved

protocol, with Good Clinical Practice (GCP), and with applicable regulatory requirements.
Data analysis will take place within the data safe haven where the video and audio data, and observational notes will be stored on a secure server in password protected folders. Data analysis will be supervised by an experienced qualitative researcher and consultant level surgeons at Sheffield Teaching Hospitals NHS Trust and Hull University Teaching Hospitals NHS Trust. Therefore, once data has been fully anonymised, and analysed it will be transferred, via secure data transfer to the two sites for checking.

Participants will be informed about what data will be collected and held on file, that these data may be viewed by the Sponsor and by external auditors on behalf of either the sponsor or regulatory agencies. Participants will be informed that short clips from their surgery will be used for training purposes, and with their consent we will retain the data for research purposes. The video clips (likely to be 1-5 minutes in length) will not contain patient identifiable data. The video clips will be made available to NHS clinicians who have expressed an interest in participating in the Phase II/III trial (via a personal email link), and will be retained for training staff taking part in the trial.

Participants will similarly be informed that a report of the study will be submitted to the Sponsor and may also be submitted to government agencies and for publication. Patient level data will not be published in these reports, and health professionals will only be identified in such reports by their site number (e.g. surgeon A at site 1) and level of seniority. The investigators undertake to hold all personal information in confidence and in compliance with the General Data Protection Regulation (GDPR 2018). A data sharing agreement will be in place between the University of Hull and the NHS Trusts.

Study documents (paper and electronic) will be retained in a secure (kept locked when not in use) location during the study. Access to stored records is strictly controlled.

## 3.8 Archiving

Study documents will be retained for 10 years in a password protected file. All documentation at the end of the study will be stored electronically. All consent forms will be stored as PDF files. Audio files will be deleted once data analysis is complete. With patient consent, edited videos will be retained for use during the follow-on randomised controlled trial as part of surgeon training. Copies of the videos taken will be retained for secondary research (with patient permission).

## 3.9 Reporting and dissemination

We aim to publish the results of this study in peer-reviewed journals as well as presenting at National conferences.

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3. Antakia, R., et al., *Effectiveness of preventative and other surgical measures on hypocalcemia following bilateral thyroid surgery: a systematic review and meta-analysis.* Thyroid, 2015. **25**(1): p. 95-106.
4. Grainger, J., et al., *Post-thyroidectomy hypocalcemia: Impact on length of stay.* Ear Nose Throat J, 2015. **94**(7): p. 276-81.
5. Dedivitis, R.A., et al., *Analysis of safety of short-stay thyroid surgery.* Acta Otorhinolaryngol Ital, 2009. **29**(6): p. 326-30.
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7. Cho, N.L., et al., *Surgeons and patients disagree on the potential consequences from hypoparathyroidism.* Endocr Pract, 2014. **20**(5): p. 427-46.
8. Nouraei, S.A., et al., *A national analysis of trends, outcomes and volume-outcome relationships in thyroid surgery.* Clin Otolaryngol, 2017. **42**(2): p. 354-365.
9. Mao, Y. and M. Xing, *Recent incidences and differential trends of thyroid cancer in the USA.* Endocr Relat Cancer, 2016. **23**(4): p. 313-22.
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