Near Infrared Fluorescence imaging to prevent post-surgical hypoparathyroidism after Thyroid surgery

NIFTy: Near Infrared Fluorescence (NIRF) Imaging to prevent Post-surgical Hypoparathyroidism (PoSH) after Thyroid Surgery (NIFTy) - A phase II/III pragmatic, multicentre randomised controlled trial

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2 CONTENTS

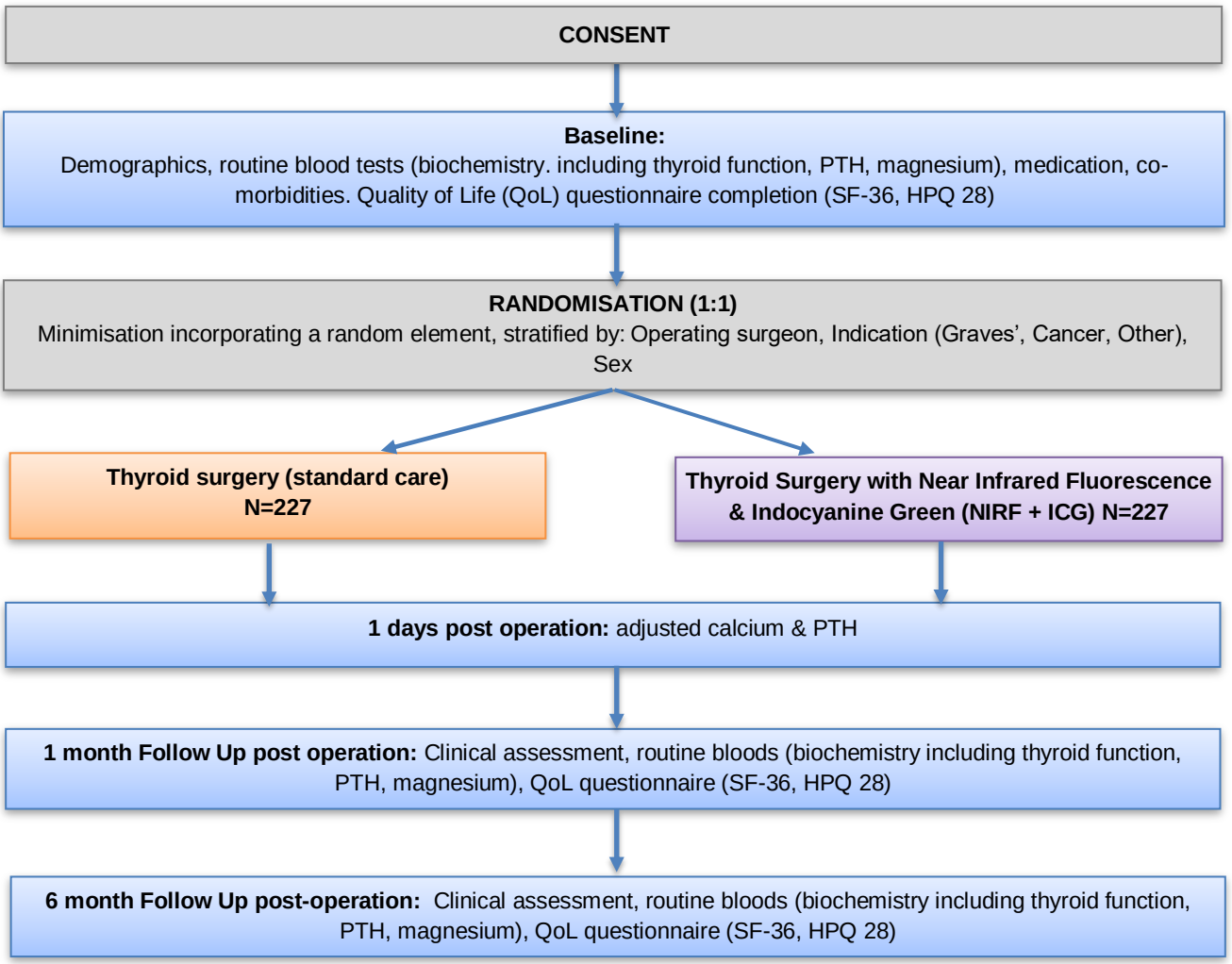
3 TRIAL SUMMARY

Trial Title	**N**ear **I**nfrared **F**luorescence (NIRF) Imaging to prevent Post-surgical Hypoparathyroidism (PoSH) after **T**hyroid Surger**y** (NIFTy) - A phase II/III pragmatic, multicentre randomised controlled trial
Trial Acronym	NIFTy
Trial Background	Post-surgical hypoparathyroidism (PoSH) is an iatrogenic disease that occurs as a complication of a number of different procedures. The vast majority of patients with hypoparathyroidism are following surgery. Thyroidectomy is the commonest predisposing operation and is performed for a range of benign and malignant conditions. The mechanisms of PoSH include devascularisation, direct damage and inadvertent removal of the parathyroid glands. PoSH has significant short and long term morbidity. In the short term, its occurrence can prolong hospital stay and is associated with multiple hospital attendances, readmission to hospital[1], 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' and a negative impact on all aspects of quality of life. Over 12,000 thyroid operations are done every year in England, a significant proportion of which involves bilateral thyroid surgery and carries a risk of this complication. The volume of thyroid surgery for both benign and malignant disease is increasing and PoSH is therefore likely to increase. Recently studies have shown promising results using a new technology, near infrared imaging (NIRF) in reducing the risk of PoSH. A significant reduction in the incidence of transient and long term hypoparathyroidism has potential to significantly reduce morbidity and costs associated with monitoring and treatment.
Trial Design	A prospective unblinded, parallel group, multicentre, seamless phase II/III randomised controlled trial comparing thyroidectomy surgery with near-infrared fluorescence (NIRF) and Indocyanine Green (ICG) against standard thyroidectomy surgery to determine the effect on 6-month post-surgical hypoparathyroidism (PoSH) in patients undergoing thyroidectomy.
Trial Aim	To determine the efficacy of NIRF imaging in reducing the risk of post-surgical hypoparathyroidism after bilateral thyroid surgery in a multi-centre randomised controlled trial comparing NIRF imaging versus standard surgery.
Trial Endpoints	**Primary endpoint:** • The primary phase II endpoint is transient hypocalcaemia, which is defined as any adjusted calcium of <2.1 mmol/L, as measured on the day after trial surgery (1 day post-operatively) • The primary phase III endpoint is the incidence of post-surgical hypoparathyroidism (PoSH) at 6 months post-surgery. **Secondary endpoints:** • Post-operative Parathyroid Hormone, as measured at 1 day post-operation, 1 month post-operation and 6 months post-operation

	• Transient hypocalcaemia: defined as per the phase II primary endpoint • Protracted hypoparathyroidism: defined as either an adjusted calcium of <2.1 mmol/L, or the need for calcium and/or vitamin D supplements to treat symptoms or maintain adjusted calcium in the low normal range (between 2.1 and 2.3 mmol/L), at 1-month post-operation. • Intra-operative complications • Post-operative complications within 6 months of operation, categorised using the Clavien-Dindo classification. • Length of post-operative hospital stay in days. • Health related quality of life (SF-36 and HPQ 28) measured at baseline, and at 1 and 6 months post-operation. • Re-admission to hospital within 6 months of surgery, for any reason • Hypercalcaemia: defined as any adjusted calcium level > 2.6 mmol/L occurring within 6 months of operation. • To explore the mechanism of the intervention by investigating the effects of the key surgical components identified in the qualitative work
Trial Population:	454 adult participants, due to undergo total or completion thyroidectomy with or without central neck dissection.
Randomisation:	Randomisation will be performed by the Clinical Trials Research Unit (CTRU), Leeds. Participants will be randomised on a 1:1 basis, using a computer-generated minimisation programme incorporating a random element, to receive standard thyroid surgery or thyroid surgery with NIRF + ICG. Minimisation Factors • Operating surgeon • Indication (Graves' disease, Cancer, Other) • Sex
Trial Intervention:	**Surgery without NIRF (standard care):** Total or completion thyroidectomy with or without central neck dissection, performed as part of standard care **Surgery with NIRF + ICG:** NIRF imaging with indocyanine green (ICG) will be used during surgery. The use of NIRF imaging will be in accordance with the protocol developed in the qualitative research (process evaluation).
Duration:	All participants will be followed up to 6 months after surgery
Evaluation of outcome measures	Participants will be assessed at 1 day, 1 month and 6 months after surgery. Quality of Life (QoL) and participant reported outcomes (assessed using the SF36 and HPQ 28) will be measured at 1 month and 6 months after surgery. Complications will be documented during trial treatment and follow-up.

4 TRIAL SCHEMA

Population: Adult patients undergoing complete or total thyroidectomy, with or without central neck dissection. (Indications for surgery may include Graves' disease, suspected or confirmed thyroid cancer, or benign pathology e.g. goitre with compressive effects). ***Inclusion criteria:*** Aged ≥ 18 years, due to undergo total or completion thyroidectomy with or without central neck dissection, ASA ≤3. ***Exclusion criteria:*** Patients undergoing concomitant parathyroid or thoracic surgery, re-operative thyroid surgery (except completion thyroidectomy after previous contralateral lobectomy), documented hypo or hypercalcaemia prior to thyroid surgery, pregnancy, intolerance or sensitivity to ICG, significant renal impairment, hepatic dysfunction, taking or due to receive peri-operative calcium or vitamin D supplements.



5 BACKGROUND

5.1 POST-SURGICAL HYPOPARATHYROIDISM

Post-surgical hypoparathyroidism (PoSH) is an iatrogenic disease that occurs as a complication of a number of different procedures. The vast majority (78-91%) of patients in the community with hypoparathyroidism are following surgery; i.e. this is primarily an iatrogenic disease [2]. Thyroidectomy is the most common predisposing operation and is performed for a range of benign and malignant conditions (e.g. multinodular goitre, hyperthyroidism, thyroid cancer). The mechanisms of PoSH include devascularisation, direct damage and inadvertent removal of the parathyroid glands [3].

PoSH has significant short and long term morbidity. In the short term, the condition 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 [1], ongoing monitoring and treatment – all significantly increasing costs of treatment. Rates of hypocalcaemia have been shown to be much higher (48%) in patients staying longer than 2 days compared to those staying less than or equal to 2 days (20%) [4].

In the long term, post-surgical hypoparathyroidism can cause a wide range of symptoms, a 'high burden of illness' [5] and a negative impact on different aspects of quality of life [6]. Epidemiological studies have also shown that these patients have an increased risk of renal impairment, seizures, infections, depression and bipolar disease [7, 8].

Over 12,000 thyroid operations are done annually in England alone (HES statistics); a significant proportion of which involves bilateral thyroid surgery and carries a risk of this complication. The volume of thyroid surgery for both benign and malignant disease is increasing in the UK [9] and worldwide, partly due to the increased detection and diagnosis of thyroid cancer [10]. The incidence and prevalence of PoSH is therefore likely to increase. A significant reduction in the incidence of transient and long term hypoparathyroidism has potential to significantly reduce morbidity and costs associated with monitoring and treatment.

5.2 EXISTING RESEARCH

Although much research has focused on the incidence [11], prevalence [7, 12, 13] and factors predisposing to this condition [14], 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 summarised in a review [11] which shows that although temporary hypocalcaemia rates may be reduced, the impact on long-term PoSH is minimal.

In the UK, the fourth national BAETS audit reports transient hypocalcaemia rates of 27% of patients undergoing bilateral thyroid surgery and the condition is expected to persist at 6 months in over 12% of patients [15]. Rates quoted in other literature range widely, partly due to a multitude of factors that may be patient, disease and surgery related [14] and partly due to the definitions of PoSH [16].The

prevalence of the problem is estimated to be around 22 per 100,000 in the Western world [7, 12]. Several factors are thought to increase the risk of the condition. These may be patient related (female sex, vitamin D deficiency), disease related (Grave's disease, large glands, retrosternal extension), surgery related (extent of surgery, lymph node dissection), local facilities, technique and expertise [14].

5.3 NEAR INFRA-RED FLUORESCENCE IMAGING TECHNOLOGY

Several novel intraoperative technologies have been investigated for their potential in identifying and preserving parathyroid glands during thyroid surgery. These include optical techniques such as fluorescent imaging, optical coherence tomography and raman spectroscopy [17] and non-optical techniques such as electrical impedance spectroscopy [18]. Of these, the most commonly investigated modality is near infra-red fluorescent (NIRF) imaging; which is based on either parathyroid auto-fluorescence or on the use of exogenous fluorophores such as indocyanine green (ICG) [19] .

The NIFTy trial will involve the use of near infrared imaging devices, specifically designed, and CE marked, for thyroid and parathyroid surgery. These hand held devices take video and still images of the inside of patients' necks. The camera contains a laser with white light emitting diodes and a charge-coupled device camera allowing the parathyroid glands inside the central compartment of the neck to be made visible. Parathyroids exhibit auto-fluorescence in the near infrared range, but the mechanism underlying this has not yet been delineated. To study parathyroid vasculature and perfusion, a short acting dye can be administered intravenously. The NIRF imaging devices detect both auto-fluorescence and Indocyanine-Green (ICG) based fluorescence, both of which are in the near infrared spectrum. ICG has been used in humans for decades in various settings and has a proven high safety profile and the toxic level dose is well documented. ICG in the blood vessels supplying the parathyroid glands emits fluorescence that can aid the surgeon in assessing the viability of the parathyroid glands.

5.4 RATIONALE FOR NIFTY

Recently completed animal [20] and phase I studies [21] show that NIRF imaging technology has potential in reducing the risk of PoSH. The doses of fluorophores such as MB and ICG for optimum fluorescence have been described and the potential for use of both auto-fluorescence and dye or contrast based fluorescence has been highlighted in the early studies [21, 22]. The potential for NIRF imaging in parathyroid preservation has been corroborated by other early phase studies [23-25] and summarised in a recent review [26]. Although the results are promising, the results are considered preliminary and need to be validated in well-conducted, multi-centre phase II and III studies.

6 AIMS AND OBJECTIVES

6.1 AIM

The aim of the study is to determine the efficacy of near infra-red fluorescence (NIRF) imaging (with Indocyanine Green) in reducing the risk of post-surgical hypoparathyroidism after bilateral thyroid surgery in a multi-centre randomised controlled trial comparing NIRF imaging versus standard surgery.

6.2 OBJECTIVES

Phase II objective
The primary objective of the Phase II component is to determine whether to continue to recruit to the Phase III component of the trial, or whether to conclude the trial on the basis of futility. This decision will be based on early assessments of efficacy measured in terms of 1-day post-operative hypocalcaemia.

Phase III objectives
The primary objective of the Phase III trial is to investigate the efficacy and mechanism of a new intervention, the use of NIRF + ICG during thyroidectomy, in reducing the rate of post-operative hypoparathyroidism (PoSH) compared to standard thyroidectomy at 6 months post-surgery.

Secondary objectives are to compare the following in the two arms of the study:

1. Post-operative Parathyroid Hormone (PTH) levels
2. Incidence of transient hypocalcaemia
3. Incidence of protracted hypoparathyroidism
4. Intra- and post-operative complications
5. Length of stay in hospital after surgery
6. Patient quality of life
7. Re-admission to hospital
8. Incidence of hypercalcaemia
9. To explore the mechanism of the intervention by investigating the effects of the key surgical components identified in the qualitative work.

6.3 OUTCOMES

Phase II primary outcome: Transient hypocalcaemia, defined as any adjusted calcium of <2.1 mmol/L on the day after surgery.

Prophylactic calcium supplements must not be given to patients before assessment of calcium levels on the day after surgery, as this can affect the validity of the 1-day endpoint.

Phase III primary outcome: Incidence of post-surgical hypoparathyroidism (PoSH) at 6 months post-surgery – defined as need for calcium and/or vitamin D supplements to treat symptoms or maintain adjusted calcium in the low normal range (between 2.1 and 2.3 mmol/L). This is in accordance with the national British Association of Endocrine and Thyroid Surgeons (BAETS) definition [15].

Phase III key secondary outcome: Post-operative PTH over 6 months after surgery

Phase III secondary outcomes: To compare NIRF + ICG and standard care in terms of:

- Transient hypocalcaemia
- Protracted hypoparathyroidism at 1-month post-operation
- Intra-operative complications
- Post-operative complications within 6 months of operation
- Length of stay in hospital post-surgery
- Health related quality of life (HRQoL) at baseline, 1-month post-operation and 6 months post-operation.
- Any episode of re-admission to hospital within 6 months of operation

- Hypercalcaemia occurring within 6 months of operation

Phase III mechanistic outcome: To explore the effect of treatment–related decision-making on patient outcomes.

7 DESIGN

An unblinded, parallel group, multicentre, seamless phase II/III randomised controlled trial comparing thyroidectomy surgery with near-infrared fluorescence (NIRF) and Indocyanine Green (ICG) against standard thyroidectomy surgery to determine the effect on post-surgical hypoparathyroidism (PoSH) at 6 months in patients undergoing thyroidectomy.

The trial is designed as a phase III trial with an interim analysis (termed hereafter as the phase II analysis) to allow the trial to stop early for futility. The phase II analysis will be performed once 1-day post-operative data is available for 200 patients (100 per treatment group), and recruitment will continue whilst the Phase II analysis is ongoing. The trial will continue beyond the phase II analysis only if there is sufficient evidence of superiority (as defined in section 15.2.1) of the experimental treatment when compared to the control; else the study will stop, concluding futility. In the event that the trial proceeds to the final phase III analysis, recruitment will continue until the full sample size of 454 patients (227 per treatment group) is reached. In both the phase II and III stages of the study participants will be randomised, prior to their surgery, to either standard thyroid surgery or thyroid surgery using NIRF and ICG on a 1:1 basis using minimisation (with a random element) – see section 9.4.3.

All trial participants, (phase II and phase III) will be followed up for 6 months after their operation.

8 ELIGIBILITY

8.1 RESEARCH SITE ELIGIBILITY

The trial will open in at least 10 research sites in the UK. Each site must fulfil a set of pre-specified criteria and complete a registration form to verify that the site is willing and able to comply with the trial requirements. This will be signed by the proposed local Principal Investigator (PI) on behalf of all staff who will be affiliated with the trial. Research sites will be required to obtain local confirmation of capacity and capability, return all required essential documentation to CTRU and undertake a site initiation with the CTRU prior to the start of recruitment into the trial.

Participation of research sites will be dependent upon the following criteria:

1. Ability to perform thyroid surgery using NIRF technology
2. Predicted capability to recruit a minimum of 12 patients per year into the NIFTy trial.

8.2 SURGEON ELIGIBILITY

Prior to randomising participants, all participating surgeons must fulfil the following criteria:

1. Surgeons must have observed at least one thyroid/parathyroid operation performed using NIRF and ICG
2. Surgeons must have performed a minimum of 5 thyroid/parathyroid operations using NIRF and ICG.
3. Surgeons must perform a minimum of 20 thyroid operations per year[1].

Observations can occur at sites experienced in using NIRF technology in this setting, for example sites that participated in the process evaluation study, or by observing a local surgeon with the relevant experience as highlighted in point 2 above.

The trial will be registered with the NIHR Associate PI (API) Scheme: (https://www.nihr.ac.uk/documents/associate-principal-investigator-pi-scheme/25040. APIs must be able to contribute to the trial for at least 6 months. Please contact the CTRU to discuss the inclusion of APIs at sites.

8.3 PATIENT ELIGIBILITY

Eligibility waivers to inclusion/exclusion criteria are not permitted. Participants must meet all of the inclusion criteria and none of the exclusion criteria.

8.3.1 INCLUSION CRITERIA

1. Aged ≥ 18 years
2. Able to provide written informed consent
3. Due to undergo total[2] 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).
4. ASA </= 3
5. Able and willing to comply with the terms of the protocol including participant completed questionnaires

8.3.2 EXCLUSION CRITERIA

1. Patients undergoing concomitant parathyroid or thoracic surgery
2. Patients undergoing re-operative thyroid surgery (except completion thyroidectomy after previous contralateral lobectomy)
3. Documented hypo or hypercalcaemia within the last 3 months prior to planned date of thyroid surgery

[1] Participating surgeons will be asked to provide the number of thyroid operations performed in the last 2 years

[2] Near-total thyroidectomy (a minor variant of thyroid surgery) is considered as 'total' thyroidectomy in the study and therefore eligible for participation

4. Pregnancy[3]
5. Known allergy to ICG, iodine or iodine dyes
6. Patients with significant renal impairment (defined as eGFR <40ml/min/1.73m^2 (or a serum creatinine value[4] >10% of upper value for normal institutional limits if eGFR is not performed locally)
7. Hepatic dysfunction, defined as bilirubin outside of institutional limits and/or ALT/AST >2.5 x institutional upper limit of normal.
8. Taken calcium or active vitamin D supplements (such as alfacalcidol or calcitrol) in the 2 weeks prior to randomisation or due to receive prophylactic treatment with calcium and/or vitamin D supplements peri-operatively

8.3.3 CONCURRENT CLINICAL TRIALS

A clinical trial is considered concurrent if the trial procedures occur, or are likely to occur, within 28 days prior to the NIFTy operation, during the NIFTy operation, or during the 6 month post operative follow-up period of NIFTy.

Participation in concurrent clinical trials will be considered on a trial-by-trial basis. However, please note that participants will not be eligible for entry into concurrent clinical trials of surgical technique, which includes any other trial that would preclude delivery of either of the NIFTy interventions as defined in either section 10.3 or the protocol developed in the qualitative research (process evaluation).

In all cases where enrolment to a concurrent clinical trial is under consideration, please contact the Clinical Trials Research Unit (CTRU, University of Leeds) in the first instance to discuss participant co-enrolment further.

9 RECRUITMENT PROCESS

9.1 RECRUITMENT SETTING

Participants will be recruited from approximately 10 research sites in the UK. Research sites will be required to confirm capacity and capability and undertake a site initiation meeting with the CTRU prior to the start of recruitment into the trial.

A total of 454 participants (227 in each arm) will be recruited into the trial over a 32-month period. A Phase II interim analysis will be performed after Phase II primary endpoint data (transient hypocalcaemia on the day after surgery) has been collected for 200 patients.

[3] It is the local surgeon's responsibility to ensure this is assessed in women of child-bearing potential according to local standard of care

[4] eGFR is the preferred method of renal function assessment, however if eGFR calculation is not performed locally, the serum creatinine measure can be used to assess renal function

9.2 ELIGIBILITY SCREENING

All patients presenting to thyroid clinics being considered for total or completion thyroid surgery should be considered for the trial.

Participating research sites will be required to maintain a log of patients, who are not randomised, either because they are ineligible or because they decline participation. Reasons for ineligibility or declining participation will be closely monitored by the CTRU as part of a regular review of recruitment progress. Non-randomisation logs should be returned to the CTRU on a quarterly basis. Anonymised information will be collected including:

- Age
- Sex
- Ethnicity
- Indication
- Considered for total or completion thyroidectomy
- Central neck dissection
- ASA grade
- Date screened
- Reason not eligible for trial participation, or
- Eligible but declined and reason for this, or
- Other reason for non-randomisation

9.3 INFORMED CONSENT

Patients requiring total or completion thyroidectomy will be identified in the surgical clinic at the time of consideration for surgery.

Suitability for inclusion into the trial will be assessed according to the eligibility criteria and potential participants will be approached in the surgical clinic. A verbal explanation of the trial along with the approved PIS/ICF will be provided by a suitably qualified member of the healthcare team for the patient to consider. The PIS will provide detailed information about the rationale, design and personal implications of the trial.

Patients may also be identified from surgical waiting lists after attending for their pre-operative assessment. Patients identified in this way will be contacted by letter, including a copy of the PIS, and will have the opportunity to discuss the trial during a phone call with the surgeon.

Following information provision, patients must be given the opportunity to discuss the trial with their family and healthcare professionals before they are asked whether they would be willing to take part in the trial. Patients will be given as much time as possible to consider their participation in the trial and ideally a minimum of 24 hours. The right of the patient to refuse participation without giving reasons must be respected.

Assenting patients will be formally assessed for eligibility either during their surgical pre-assessment clinic appointment or at another time prior to the surgery, and invited to provide informed, written consent for their participation in the trial, including explicit consent for the transfer of a copy of their signed consent form to the CTRU.

Informed consent may only be obtained by the Principal Investigator (PI) or an appropriate, delegated, healthcare professional. Healthcare professionals' who have delegated responsibility to participate in the informed consent process must have knowledge of the trial interventions and have received training in the principles of GCP and the Declaration of Helsinki 1996. They must be fully informed of the ethically approved protocol and be authorised and approved by the PI to take informed consent as documented in the trial APL. The PI retains overall responsibility for the informed consent of participants at their research site.

The patient consent form with all original signatures must be retained in the ISF. A copy of the signed consent form must be given to the participant, and a record of the consent process, detailing the date of consent and witnesses, must also be kept in the participant's medical notes (this may include a copy of the consent form as per local practice). A copy of the signed consent form must also be transferred to the CTRU.

Participants will remain free to withdraw from the trial at any time without giving reasons and without prejudicing any further treatment.

9.3.1 TIMING OF CONSENT

Written informed consent should be obtained as close to randomisation as possible, but must be prior to randomisation.

9.3.2 LOSS OF CAPACITY FOLLOWING INFORMED CONSENT

Loss of mental capacity of a participant after giving informed consent for the trial is expected to be a rare occurrence. Should this eventuality occur, this should be reported to the CTRU by completing the withdrawal eCRF on the NIFTy database **within 7 days** of site becoming aware and no further trial procedures or data collection should occur from this point onwards. Any data collected up to the point of withdrawal will be kept on record and used in the trial analysis.

9.4 RANDOMISATION

9.4.1 TIMING OF RANDOMISATION

Randomisation should take place as soon as possible after consent is obtained and participants have completed their baseline participant-completed questionnaires (see section 11.9). To avoid bias in questionnaires occurring due to patient knowledge of randomisation allocation, baseline participant-completed questionnaires must be completed after the participant has provided written informed consent and prior to randomisation, if this is not possible, these must be completed prior to the participant being made aware of the treatment allocated at randomisation. Randomisation should take place as close to the to the planned surgery date as possible and no more than 4 weeks before.

9.4.2 RANDOMISATION PROCESS

Following confirmation of written informed consent, eligibility, and completion of the baseline participant-completed questionnaires (wherever possible), participants will be randomised into the trial by an authorised member of staff at the research site. Randomisation will be performed centrally using the

CTRU automated 24-hour randomisation system, accessed by sites via the CTRU website. Authorised personnel will be provided PIN codes to use alongside their email address to access the 24-hour randomisation service.

The following information will be required at randomisation:

- Participant details, including initials and date of birth
- Name and code of the research site
- Name of the person making the randomisation
- Name of the treating surgeon
- Confirmation of eligibility
- Confirmation of written informed consent
- Minimisation factors (see section 9.4.3)
- Planned date of the operation

To randomise participants using the 24 hour randomisation system visit the web page: https://lictr.leeds.ac.uk/webrand/

After randomisation, complete the participant's contact information on the Contact Form required for quality of life administration and send to the CTRU along with a copy of the consent form.

9.4.3 TREATMENT ALLOCATION

Participants will be randomised on a 1:1 basis to receive thyroid surgery performed either as per standard care or with NIRF imaging + ICG, and will be allocated a unique 5-digit trial number. A computer-generated minimisation programme that incorporates a random element will be used to ensure treatment groups are well-balanced for the following participant characteristics, details of which will be required for randomisation:

- Operating surgeon
- Indication (Graves', Cancer, Other)
- Sex

10 INTERVENTION DETAILS

10.1 SCHEDULE OF CLINICAL ASSESSMENTS/DATA COLLECTION POINTS

The timing of clinical assessments and data collections points are summarised in Table 1 overleaf. All participants will be followed up via clinic visits as per protocol until 6 months after surgery.

Table 1: Schedule of Events

	Events	Baseline/ Pre-op	Surgery	1 day post-op	1 month post-op	6 month post-op
Clinical Assessments/ investigations	Clinical examination	✓		✓	✓	✓
	Biochemistry	✓		✓	✓	✓
	Trial Consent	✓				
	Operative details		✓			
	Complications		✓		✓	✓
Data collection time points	Eligibility eCRF	✓				
	Randomisation eCRF	✓				
	Baseline eCRF	✓				
	Operative eCRF		✓			
	1 day after surgery f/up eCRF			✓		
	1 month after surgery f/up eCRF				✓	
	6 month after surgery f/up eCRF					✓
HRQoL	SF-36	✓			✓	✓
	HPQ 28	✓			✓	✓

10.2 Baseline/Pre-Operation Investigations and Preparation

Pre-operative investigations and preparation will be as per institutional protocol. A biochemical assessment will be carried out including; thyroid function, renal function, calcium, PTH, vitamin D, magnesium, phosphate, LFTs and U&Es, details of which will be recorded on the trial CRFs.

Patients enrolled in the study **must not** be given prophylactic treatment with calcium and/or vitamin D supplements peri-operatively. However, any vitamin D deficiency that is detected during investigation may be treated as per local protocols.

10.3 Intervention Details

10.3.1 Surgery without NIRF imaging (Standard care)

For participants randomised to the surgery without NIRF imaging (standard care) arm, the total or completion thyroidectomy, with or without central neck dissection, should be performed as part of standard care.

10.3.2 Surgery with NIRF imaging and ICG

For participants randomised to the surgery with NIRF + ICG arm, the total or completion thyroidectomy, with or without central neck dissection, will be performed using NIRF imaging with and without ICG during surgery. The use of NIRF imaging will be in accordance to the protocol developed in the qualitative research (process evaluation) and detailed in the NIFTy Surgical Manual.

10.4 Post-Operative Care

Post-operative care will be in accordance to local and national protocols and guidance and will include an evaluation for hypocalcaemia/hypoparathyroidism by review of symptoms and biochemistry. Most patients will be discharged 1-2 days after their surgery.

Participants will be reviewed at:

- 1 day after surgery (inpatient)
- 1 month after surgery (outpatient clinic)
- 6 months after surgery

Any further visits will be according to local clinical practice.

11 DATA COLLECTION

11.1 PARTICIPATING SURGEON DATA

Data on surgeon experience will be recorded for all participating surgeons at the point of entry into the trial, including the total number of relevant thyroidectomy procedures performed, both with and without the use of NIRF technology, and the number of thyroid operations performed during the last 2 years. This will be in addition to ongoing collection of surgeon experience throughout the trial period (including relevant experience gained outside of the trial).

11.2 TRIAL PARTICIPANT DATA

Participating research sites will be expected to maintain a file of essential trial documentation (Investigator Site File), which will be provided by the CTRU, and keep copies of all completed paper CRFs for the trial.

Clinical data will be collected at baseline, operation, and at 1 day, 1 month and 6 months after surgery; participant-completed data will be collected at baseline and at 1 and 6 months after surgery.

Case Report Forms (CRFs), electronic CRFs (eCRFs), and participant-completed questionnaires will contain the participant's unique trial number, date of birth, and initials.

11.3 SUBMISSION OF TRIAL DATA

CTRU will provide electronic copies of trial-specific paper case report forms (CRFs) required for collection of informed consent, contact information and serious complication data (SCs/USCs) requiring expedited reporting (see section 12.3.2). Baseline participant completed questionnaires will be collected on paper, with follow up participant completed questionnaires collected either on paper or electronically via patient reported outcome software dependent on participant choice.

Trial data collected on paper CRFs will be completed by participating sites and submitted to the CTRU usually via standard post (but sometimes via email, fax or secure electronic transfer). If Informed Consent Documents are posted to CTRU, they must be sent in a separate envelope to other forms.

All other data collection will be via Remote Data Entry (RDE) on electronic case report forms (eCRFs) managed by the CTRU at the University of Leeds. Access to the live NIFTy database will be provided by the CTRU following sites authorisation to open to recruitment; An SSOP will offer guidance on RDE and completing eCRFs. Missing and discrepant data will be flagged and additional data validations raised as appropriate from the CTRU data management team.

Data must only be completed by personnel authorised to do so by the PI, as recorded on the trial-specific Authorised Personnel Log.

11.4 PRE-TREATMENT DATA COLLECTION

Participants must be screened, assessed for eligibility and have provided written informed consent before they can then be randomised (Sections 9.3.1 and 9.4.1)
Data collected on the pre-treatment CRFs (Eligibility Checklist, Baseline and Randomisation Forms) will include (but will not be limited to):

- Personal details, demographics including height, weight, gender, and American Society of Anesthesiologists (ASA) grade (I, II, III),
- Medical history including previous neck surgery, history of calcium related illness, indication for surgery, thyroid imaging results, presence of retrosternal extension
- Pre-operative treatment; current & recent (last 3 months) medications including ongoing calcium & vitamin D supplements
- Results of pre-treatment investigations, calcium, PTH, vitamin D, magnesium, phosphate, renal function, TSH, LFTs, U&Es
- Other information required to confirm eligibility

Following written informed consent and wherever possible prior to randomisation (where this is not possible this must be prior to the participant being made aware of their randomised treatment) participants will also be asked to complete the baseline participant-completed questionnaires:

11.5 OPERATIVE DATA COLLECTION

An operative CRF will be completed which will collate data relating to the surgical operation including (but not limited to):

- Operating surgeon
- Performed operation
- Extent of thyroid and lymph node surgery
- Use of energy devices
- Use of nerve monitoring
- Operative decision making related to use of NIRF+ICG (NIRF+ICG group only):
- Any intra-operative complications[5]

[5]Some complications will require expedited reporting to CTRU, please see Section 12 for more details

11.6 One Day Post-Operative Data Collection

Prophylactic calcium supplements must not be given to participants prior to the assessment of hypocalcaemia on the day after surgery as this can affect the validity of the 1-day endpoint.

11.6.1 Data Collection (1 day post-op)

All participants will be assessed on the day after surgery for Transient hypocalcaemia. Data collected at the 1 day post-operative assessment will include:

- Adjusted calcium
- PTH

11.6.2 Transient Hypocalcaemia

Transient hypocalcaemia is defined as any adjusted calcium of <2.1 mmol/L.

The detection and treatment of acute post-thyroidectomy hypocalcaemia will be performed as per local protocols. A protocol developed and validated in the Sheffield unit may be used as a guide for participating sites if required (see Appendix 1).

11.7 Follow-Up Data Collection

11.7.1 Data Collection for clinical assessments

Participants will be assessed during their follow up period for incidence of transient hypocalcaemia, protracted hypoparathyroidism, PoSH and hypercalcaemia. All participants will have a clinic assessment at around 1 month and 6 months after surgery.

Data collected during follow up will include (but will not be limited to):

- Adjusted calcium
- Need for calcium/Vitamin D supplements
- Incidence of PoSH
- Calcium and Vitamin D dose
- Number of calcium blood tests
- Biochemistry (magnesium, PTH, Phosphate, TSH)
- Hypothyroidism
- Number of clinic visits
- Length of stay

- Post-operative complications[6], and severity (see section for 12.3.1 classification)
- Re-admissions to hospital
- Participant Quality of Life (See section 11.9)

11.7.2 POST-SURGICAL HYPOPARATHRYOIDISM (POSH)

Hypoparathyroidism is defined as need for calcium and/or vitamin D supplements to treat symptoms or maintain adjusted calcium in the low normal range (between 2.1 and 2.3 mmol/L).

Monitoring and treatment of PoSH will be performed as per local protocols. A protocol for monitoring and treatment of PoSH has been developed for the trial for participating sites to use as guidance if required (see Appendix 1).

11.8 END OF FOLLOW-UP

Participants are followed up for 6 months after their trial operation. The trial follow up period will end 6 months after the last trial operation, once all trial participants have been confirmed as having or not having an operation[7].

11.9 PARTICIPANT COMPLETED QUESTIONNAIRES

Participants will be asked to complete a questionnaire booklet at baseline and, 1 and 6 months after surgery. The following questionnaires will be included in the booklet.

- **SF-36®**: A validated generic health survey which asks 36 questions across 8 health domains to measure functional health and well-being.
- **HPQ 28**: A disease characteristic questionnaire with 28 items across 5 domains to measure characteristic symptoms and quality of life.

The baseline questionnaire booklet will be completed at the participating research site, administered by the research staff/nurse. Participants will be asked to seal their completed baseline questionnaire pack in a pre-supplied envelope prior to giving it to the local research staff, who will then send the sealed envelope to the CTRU for entry into the trial database.

Subsequent questionnaire booklets (1 and 6 months after surgery) will be administered to the participants by the CTRU trial team. Participants can choose whether to complete the questionnaires on paper or electronically. Participants who have chosen paper versions, will receive the questionnaire packs from the CTRU trial team by post and asked to return the completed questionnaires to the CTRU

[6]Some complications will require expedited reporting to CTRU, please see Section 12 for more details

[7] Where no operative form is received, or confirmation that a participant is not having an operation is not received by 6 months after the last randomisation, participants will be classed as not having had an operation.

using a pre-supplied stamped, addressed envelope. For participants who choose to complete the questionnaires electronically SMS and/or emails will be sent to the participants from the CTRU with a link to the questionnaire and to prompt completion. A 'thank you' message will be sent to participants by the CTRU upon receipt of a completed questionnaire. If a completed questionnaire is not received at the CTRU by the required time-point, the CTRU will send one reminder to the participant either by post, text or email (depending on the participant's preferences).

Due to the nature of some questions in the questionnaires, if CTRU are concerned by any *additional* information that may have been volunteered by the participants, that the participant may be a danger to them self, the CTRU will alert the local research team.

11.10 PREGNANCY

Any suspected or confirmed pregnancies between the date of randomisation and the date of surgery must be reported to the CTRU using the Notification of pregnancy eCRF on the NIFTy database **within 7 days** of the research site becoming aware. All further trial mandated treatment must be stopped immediately if a pregnancy occurs or is suspected during this time; it is the responsibility of the treating surgeon to decide what course of action should be taken in relation to ensuring the participant's ongoing treatment outside of the trial protocol.

The CTRU will inform the Sponsor of all reported pregnancies.

11.11 PARTICIPANT WITHDRAWAL

In line with usual clinical care, cessation or alteration of treatment at any time will be at the discretion of the attending clinician or the participant themselves.

In the event that a participant withdraws prior to randomisation, no further data is required to be submitted.

If a participant withdraws after randomisation (prior to, or after their operation) participants will still attend for follow-up assessments unless unwilling to do so, and CRFs will continue to be completed.

The PI, or delegate should make every effort to ensure that the specific wishes of any participant who wishes to withdraw consent to further involvement in the trial are defined and documented using the withdrawal eCRF on the NIFTy database **within 7 days** of the withdrawal request. This is to ensure that the correct processes are followed by the CTRU and research site following the withdrawal of consent.

11.12 DEATH

Deaths that occur during the participant's 6 month follow up period must be reported to the CTRU using the Notification of Death eCRF on the NIFTy database **within 7 days** of site becoming aware of the event. Data collected will include (but will not be limited to):

- Date of death
- Cause of death

11.13 Definition of End of Trial

The end of the trial is defined as the date of the last participant's last data item.

11.14 Protocol Deviations

The CTRU undertake to adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of the CTRU. All such deviations will be documented on the study records, together with the reason for their occurrence; where appropriate, deviations will be detailed in the published report.

12 SAFETY REPORTING

For the purpose of this surgical trial, the safety reporting terms adverse events and serious adverse events have been translated into complications.

12.1 General Definitions

A **complication** is defined as an untoward medical event in a participant, which has a causal relationship to the trial. The trial includes the trial intervention as defined in section 10.3 and any further treatment related to the trial intervention (such as treatment of complications caused by the trial intervention and any trial-related interventions e.g. the consent process and completion of questionnaires).

An untoward medical event can include:

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing condition
- any clinically relevant deterioration in any tests performed

A **serious complication (SC)** is defined as a complication which:

- results in death

- is life-threatening[8]
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect, or
- is otherwise considered medically significant by the investigator

An **Unexpected Serious Complication (USC)** is a **serious** complication which is **related** and **unexpected** and will require expedited reporting (see section 12.3.2) to enable reporting to the main Research Ethics Committee (REC) and Sponsor.

The Health Research Authority (HRA) defines the terms **related** and **unexpected** as:

- **Related**: that is, it resulted from administration of any research procedures. All complications by definition are related to the trial procedures. (Untoward medical events which are unrelated to the trial procedures are not being collected in this trial.)
- **Unexpected**: that is, the type of event that in the opinion of the investigator is not considered expected (or is an unexpected severity of an expected complication). Examples of expected complications are provided in section 12.2; note this is not an exhaustive list.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see section 12.4 for Responsibilities). These characteristics/consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

12.2 Expected Complications

Related to thyroidectomy

- Bleeding
- Wound infections or healing problems
- Damage to adjacent organs or structures
    - Recurrent laryngeal nerve injury with potential problems such as voice / swallowing difficulty, breathing problems. This could be transient or permanent, unilateral or bilateral. If bilateral, there is a potential for tracheostomy and complete voice loss
    - Parathyroid glands – causing transient or long term hypocalcemia and/or hypoparathyroidism
    - Tracheal injury
    - Esophageal injury

[8] Life-threatening refers to an event in which the participant was at risk of death at the time of the event, NOT an event which hypothetically may have caused death had it been more severe.

- Excessive scarring
- Potential for reoperation or intervention – either for infection, bleeding, any of the above complications, persistent or recurrent disease
- Cardiac, vascular and/or respiratory complications
  - Cardiac – arrhythmia, cardiac failure, ischemic heart disease or myocardial infarction
  - Respiratory – respiratory failure, aspiration, pleural effusion, chest infection or pulmonary embolus
  - Vascular – damage to major vessels, deep vein thrombosis

Related to ICG administration

- Anaphylactoid reactions – pruritis, urticaria, bronchospasm, flushing
- Anaphylaxis

12.3 Reporting of Complications

Information on all complications will be collected for this trial whether volunteered by the participant, or detected by investigator on questioning, physical examination or other investigations.

12.3.1 Classification of complications

All complications should be graded using the Clavien-Dindo Classification scale [27] where appropriate (see Appendix 2)

12.3.2 Unexpected Serious Complications (USCs) and Serious Complication (SCs) related to ICG occurring within 30 days of the operation – Expedited reporting

All Unexpected Serious Complications (USCs) occurring within 30 days of the operation are subject to expedited reporting requirements and must therefore be notified to the CTRU **within 24 hours** of the clinical research staff becoming aware of the event.

Serious Complications (SCs) with a **causal relationship to ICG** or **ICG administration** occurring within 30 days of the operation are subject to expedited reporting requirements and must therefore be notified to the CTRU **within 24 hours** of the clinical research staff becoming aware of the event.

Notifications must be sent to CTRU by fax or email using the SC / USC CRF. Once all resulting queries have been resolved, the CTRU will request the original form is posted to the CTRU and a copy retained at site.

See section 12.1 for complication definitions

24 hr fax for reporting SC & USCs: 0113 343 6774 or Email NIFTy@leeds.ac.uk

For each SC and USC, the following data will be collected:

- Start and end dates of event, if resolved
- Full details of complication in medical terms with a diagnosis (if possible)
- Action/intervention
- Outcome
- An identifiable and authorised reporting source (i.e. the signature of the investigator or other medic authorised by the investigator at the reporting research site)

Any follow-up information on SCs and USCs must be faxed or emailed to the CTRU as soon as it is available. Events will be followed up until resolution or a final outcome has been reached. All reportable SCs and USCs will be reviewed by the Chief Investigator (CI) and will be subject to expedited reporting to the Sponsor and the REC by the CTRU on behalf of the CI in accordance with current HRA guidance, CTRU Standard Operating Procedures (SOPs), and Sponsor requirements.

SCs and USCs with an onset date greater than 30 days after surgery are not subject to expedited reporting, but must be reported with all other types of complications (i.e. non-serious expected and unexpected complications and serious complications not related to ICG) via the follow-up assessment eCRFs, as appropriate (See section 11.7).

12.3.3 ALL OTHER COMPLICATIONS – NON-EXPEDITED REPORTING

Information about the incidence and severity of all other complications (this includes all non-serious expected and unexpected complications) which occur from the date of randomisation until 6 months after surgery will be collected for all participants on the operative and follow-up assessment eCRFs, as appropriate (See section 11.7). This also applies to SCs or USCs with an onset date greater than 30 days after surgery. These events will **not** be subject to expedited reporting requirements.

12.3.4 UNTOWARD MEDICAL EVENTS UNRELATED TO THE TRIAL – NOT REPORTABLE

It is anticipated that there will be minimal additional risks associated with the interventions in this trial. Participants treated may have co-morbidities and in recognition of this, untoward medical events will only be reported if they are classified as related to trial procedures (including the surgical intervention and related procedures or trial-specific procedures such as consent and questionnaire completion).

12.4 Responsibilities For Safety Reporting

Principal Investigator (PI) (i.e. lead trial clinician at each recruiting research site or appropriate clinical individual identified in the APL)

- Checking for complications during admission and follow-up, including judgment in assigning:
    - Causality, i.e. whether an untoward medical event is related (i.e. a complication which therefore needs to be reported) or unrelated (i.e. not a complication and therefore does not need to be reported)
    - Seriousness
    - Expectedness
- To ensure ICG related SCs and all USCs occurring during participants' 30-day post-operative period are recorded and initially reported to the CTRU within 24 hours of the research site team becoming aware and to provide further follow-up information as soon as available.
- To report all other complications (serious complications unrelated to ICG, SCs and USCs occurring beyond 30 days after surgery, and non-serious complications) to the CTRU in line with the protocol during the trial follow-up period.
- To report USCs to local committees in line with local arrangements.

Chief Investigator (CI) (or nominated individual in CI's absence)

- Assign relatedness and expected nature of reported complications/untoward medical events where it has not been possible to obtain local assessment.
- Undertake review of SCs and USCs (see section 12.3.2).
    - In the event of disagreement between local assessment and the CI, local assessment may be upgraded or downgraded by the CI prior to reporting to the REC.

Clinical Trials Research Unit (CTRU)

- Expedited reporting of USCs occurring within 30 days after surgery to the REC and Sponsor within required timelines.
- Preparing annual safety reports to the REC and periodic safety reports to the Trial Steering Committee (TSC) and Data Monitoring & Ethics Committee (DMEC) as appropriate.
- Notifying Investigators of SCs and USCs which compromise participant safety.

Expedited reporting of events (as detailed in section 12.3.2) to the REC and Sponsor will be subject to current HRA guidance, CTRU SOPs and Sponsor requirements.

Trial Steering Committee (TSC)

- Periodic review of safety data in accordance with the TSC Terms of Reference and CTRU policies, and liaising with the DMEC regarding safety issues.

Data Monitoring & Ethics Committee (DMEC)

- In accordance with the DMEC Terms of Reference and CTRU policies, periodic review of unblinded overall safety data to determine patterns and trends of events and to identify any safety issues which would not be apparent on an individual case basis.

13 ENDPOINTS

13.1 PHASE II PRIMARY ENDPOINT

The primary phase II endpoint is transient hypocalcaemia, which is defined as any adjusted calcium of <2.1 mmol/L, as measured on the day after surgery (1 day post-operatively) [28].

Prophylactic calcium supplements must not be given to patients before the assessment of hypocalcaemia on the day after surgery is made as this can affect the validity of the 1-day endpoint.

13.2 PHASE III PRIMARY ENDPOINT

The primary phase III endpoint is the incidence of post-surgical hypoparathyroidism (PoSH) at 6 months post-surgery.

In accordance with the national British Association of Endocrine and Thyroid Surgeons (BAETS) definition [28], PoSH is defined as the need for calcium and/or vitamin D supplements to treat symptoms or maintain adjusted calcium in the low normal range (between 2.1 and 2.3 mmol/L) at 6 months after surgery.

13.3 PHASE III SECONDARY ENDPOINTS

- *Key secondary endpoint of post-operative PTH*, as measured at 1 day post-operation, 1 month post-operation and 6 months post-operatively
- *Transient hypocalcaemia:* defined as per the phase II primary endpoint
- *Protracted hypoparathyroidism*: defined as either an adjusted calcium of <2.1 mmol/L, or the need for calcium and/or vitamin D supplements to treat symptoms or maintain adjusted calcium in the low normal range (between 2.1 and 2.3 mmol/L), at 1-month post-operation.

- *Intra-operative complications*
- *Post-operative complications* within 6 months of operation, categorised using the Clavien-Dindo classification.
- *Length of post-operative hospital stay* in days.
- *Health related quality of life (SF-36 and HPQ 28)* measured at baseline, and at 1 and 6 months post-operation.
- *Re-admission* to hospital within 6 months of surgery, for any reason
- *Hypercalcaemia*: defined as any adjusted calcium level > 2.6 mmol/L occurring within 6 months of operation.

13.4 PHASE III MECHANISTIC ENDPOINT

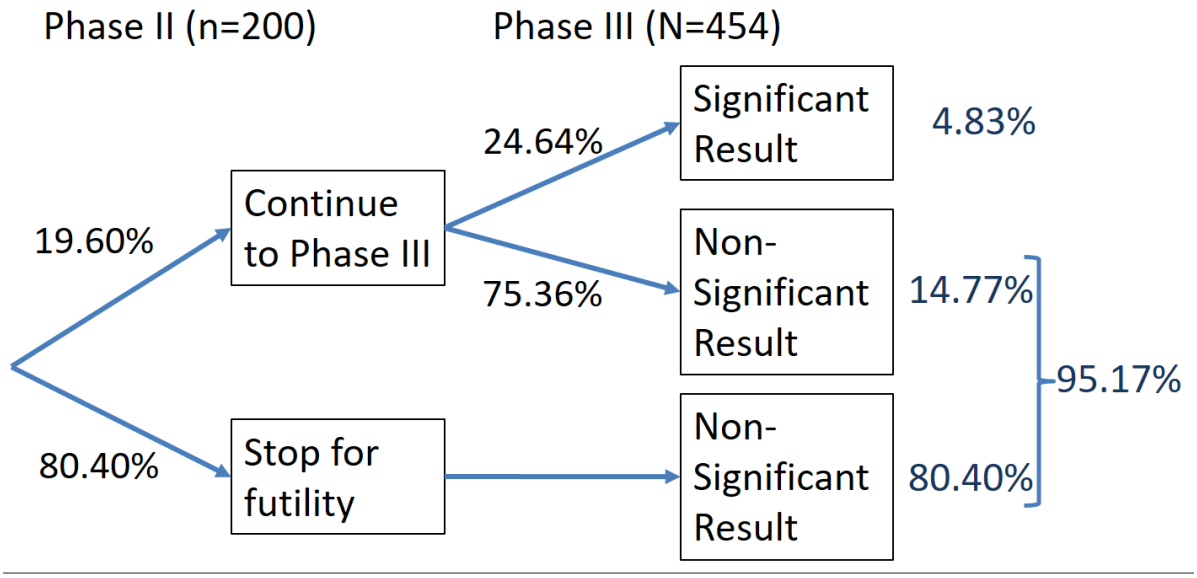
Treatment related decision making including how the intra-operative decision to perform a central neck dissection in cancer patients and to auto transplant the parathyroid glands is affected. The specific mediating and moderating factors of interest will be pinpointed via the qualitative research and included in the statistical analysis plan.

14 STATISTICAL CONSIDERATIONS

14.1 SAMPLE SIZE

Bayesian optimisation [29] was used to determine the combination of total sample size, Phase II sample size and the decision boundaries for the test statistics at the Phase II and Phase III analyses (Z_{II} and Z_{III}, see section 15 for further details on the chosen decision boundaries) that minimise the expected sample size required, whilst maintaining an overall significance level of 5% and overall power of at least 80%. Each design explored during the optimisation process was estimated empirically via simulations, using 1,000 repeats, and the operating characteristics of this chosen optimal design were re-evaluated using 100,000 repeats.

The target sample size is 454 patients (227 per treatment group), with an interim Phase II analysis after 200 patients (100 per treatment group), to allow the trial to stop early due to futility. Assuming a 6-month PoSH rate of 10% in the control group & 1-day hypocalcaemia rate of 25% in the control group and 12.5% in the experimental group, this design yields around 89% power at the 5% level of significance to detect a relative reduction in 6-month PoSH of at least 70% (i.e. a reduction to 3% 6-month PoSH in the experimental group), allowing for a 10% drop-out rate. Additionally, this sample size estimate relies on the key assumption that patients who are not hypocalcaemic at 1-day post-surgery will not have PoSH at 6 months (i.e. that the joint probability P(1-day hypocalcaemia = No, 6-month PoSH = Yes) = 0 in both treatment groups).



100,000 simulations run
Phase II stop/go rule: Z_II < -0.84162 (equivalent to one-sided alpha of 0.2)
Phase III test of difference between arms: |Z_III| > 1.28155 (equivalent to two-sided alpha of 0.2)

Figure 1: Operating characteristics of the proposed design under the null hypothesis

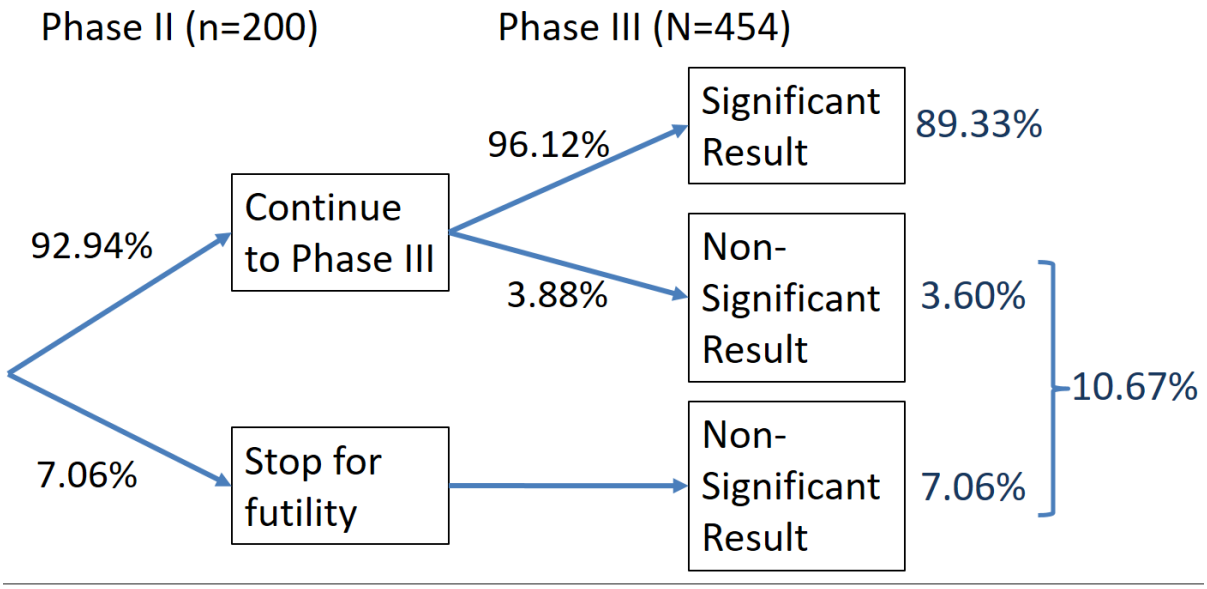


Figure 2: Operating characteristics of the proposed design under the alternative hypothesis

15 STATISTICAL ANALYSIS

Statistical analysis is the responsibility of the CTRU Statistician. A full statistical analysis plan will be written before any analyses are undertaken. Analysis and reporting will be in line with CONSORT guidance. The primary phase II and phase III analyses will be conducted using the principles of intention-to-treat (ITT), meaning that participants will be analysed in the group to which they were randomised irrespective of whether or not they receive their allocated intervention.

15.1 INTERIM ANALYSIS (PHASE II ANALYSIS)

Recruitment will continue whilst the Phase II analysis is ongoing. Results of the interim analysis will be presented to the DMEC in strict confidence. This committee, in light of the interim data, and of any advice or evidence they wish to request, will advise the Trial Steering Committee if there is proof beyond reasonable doubt that the trial should be stopped in accordance with the planned stopping rules. The interim analysis will occur once 200 patients (100 in each treatment group) have provided data on biochemistry on first postoperative day. Only the phase II primary endpoint will be assessed at the phase II analysis.

The phase II analysis will compare the 1-day hypocalcaemia rates between the arms using multi-level logistic regression, incorporating random effects with respect to surgeon and adjusting for the minimisation factors. At the phase II analysis, the trial will continue only if there is sufficient evidence of superiority of the experimental treatment compared to the control. This will be determined via a one-sided critical region for Z_{II}, the Z-value from the multi-level logistic regression model's Wald test of the adjusted log-odds ratio of 1-day hypocalcaemia. If $Z_{II} < -0.84162$ then the trial will continue, otherwise it will stop for futility. The stop/go decision at phase II will be binding.

Should the trial stop in accordance with the stopping rule defined above, the final analysis of the trial will occur once all recruited participants have completed follow-up, acknowledging any limitations that may be imposed on the trial results as a consequence of early stopping. In the event that changes to the analysis methods outlined in section 15.2 are required, these will be specified *a priori* in an amendment to the trial's statistical analysis plan.

15.2 FINAL ANALYSES (PHASE III ANALYSES)

15.2.1 PRIMARY ENDPOINT ANALYSES

The phase III analysis will compare 6-month PoSH rates between the arms using multi-level logistic regression incorporating random effects with respect to surgeon and adjusting for the minimisation factors. At the phase III analysis evidence of a difference between the treatment groups will be determined via a two-sided critical region for Z_{III}, the Z-value from the multi-level logistic regression model's Wald test of the adjusted log-odds ratio of 6-month PoSH. If $|Z_{III}| > 1.28155$ then the trial will conclude that there is a significant difference between the treatment arms.

15.2.2 SECONDARY ENDPOINT ANALYSES

Secondary endpoints with binary measures (transient hypocalcaemia, protracted hypoparathyroidism, re-admission and hypercalcaemia) will be analysed using multi-level logistic regression adjusting for the minimisation factors, incorporating random effects with respect to surgeon. Secondary endpoints with continuous measures (e.g. Post-operative PTH, length of post-operative hospital stay and HRQoL) will be analysed using multi-level generalised linear models incorporating random effects with respect to surgeon and assuming normal errors at the patient level. If the assumption of normal errors is clearly violated by the observed response data, then transformations of the response variable as well as alternative distributional assumptions will be explored, and the choice of a transformation and/or alternative distribution will be driven by comparative measures of model fit. Models for endpoints which are measured at multiple time points, will also include an additional level to account for repeated measures – i.e. repeated measures (level 1) nested within patient (level 2) nested within surgeon (level 3), so that longitudinal effects can be assessed.

16 TRIAL MONITORING

Trial supervision will be established according to the principles of GCP and in-line with the NHS UK Policy Framework for Health and Social Care. This will include establishment of a core Project Team, Trial Management Group (TMG), an independent TSC and independent DMEC. A Trial Monitoring Plan will be developed based on the trial risk assessment; this may include site monitoring.

16.1 TRIAL STEERING COMMITTEE (TSC) & DATA MONITORING AND ETHICS COMMITTEE (DMEC)

An independent DMEC will be appointed to review the safety and ethics of the trial, alongside trial progress and the overall direction as overseen by the TSC. Detailed un-blinded reports will be prepared by the CTRU for the DMEC at approximately yearly intervals.

The DMEC will be provided with detailed un-blinded reports containing the following information:

- Rates of occurrence of unexpected serious complications (USCs; see section 12.1) by treatment group
- Time between randomisation and trial treatment by treatment group for each participating research site
- Rates of operative and post-operative complications by treatment group for each participating surgeon.

Trial progress will be closely monitored by the independent DMEC, who will report to the TSC, and the overall direction overseen by the TSC (ensuring regular reports to the NIHR Efficacy and Mechanism Evaluation (EME) Programme).

16.2 DATA MONITORING

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until they are received, until confirmed as not available, or until the trial is at analysis.

The CTRU or Sponsor will reserve the right to intermittently conduct source data verification (SDV) exercises on a sample of participants, which will be carried out by staff from the CTRU or Sponsor. SDV will involve direct access to participant medical notes at the participating research sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

16.3 Clinical Governance Issues

To ensure responsibility and accountability for the overall quality of care received by participants during the trial period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual research sites.

17 QUALITY ASSURANCE, ETHICAL CONSIDERATIONS, AND CONFIDENTIALITY

17.1 Quality Assurance

The trial will be conducted in accordance with the principles of GCP in clinical trials, NHS UK Policy Framework for Health and Social Care and through adherence to CTRU SOPs.

17.2 Serious Breaches

The CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to **immediately** notify the CTRU of a serious breach (as defined in the latest version of the HRA SOP) that they become aware of. A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree-

a) the safety or physical or mental integrity of the trial subjects, or

b) the scientific value of the research

In the event of doubt or for further information, the Investigator should contact the Senior Trial Manager at the CTRU.

17.3 Ethical Considerations

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013. Informed written consent will be obtained from the participants prior to randomisation into the trial. The right of a patient to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment.

17.3.1 ETHICAL APPROVAL

Ethical approval will be sought through the Health Research Authority (HRA). The trial will be submitted to and approved by a REC, the HRA and the appropriate Site Specific Assessor for each participating research site prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, participant information sheets, consent forms and all other relevant trial documentation.

18 INFORMATION GOVERNANCE AND CONFIDENTIALITY

Sheffield Teaching Hospital Trust and the University of Leeds are joint data controllers for the trial. Participating sites will be data processors for any trial data processing (while remaining data controllers of data processing required for patient care).

All data processing for the trial will be in accordance with the 2018 Data Protection Act. Personal data will be processed under a lawful basis of 'task in the public interest' (GDPR Article 6, 1(e)) and special categories of personal data (in this case, data about health, racial or ethnic origin and genetic data) will be processed for scientific research purposes (GDPR Article 9, 2(j)).

All trial participants (and any patients considered for the trial) are provided with detailed information about how their data will be processed before any trial data processing. Any material changes to how data will be processed will be communicated to trial participants in a timely manner (prior to the changes, if reasonably possible).

Personal data will only be processed for specified, explicit and legitimate purposes, and will be adequate, relevant and limited to those purposes. Data will be stored and transferred securely for all processing. The trial will undergo an information governance risk assessment at the CTRU to ensure its proposed processing is compliant with data protection laws.

Confidentiality of participant data will be maintained at all times, with access to data granted only to those who need it for legitimate reasons (i.e. to conduct the trial, or to ensure the trial has been conducted lawfully). Participants will allow access to their confidential data through the informed consent process. Copies of participant consent forms, which will include participants' names, will be collected when a participant is randomised into the trial by the CTRU. In addition, participant name and address may be collected for questionnaire posting or email address/phone number if the participant chooses to complete the questionnaires electronically. All other data collection forms that are transferred to or from the CTRU will be coded with a unique participant trial number and will include two participant identifiers, usually the participant's initials and date of birth. Data will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRU will have access to the entire database for monitoring, co-ordinating, and analysis purposes.

Sites are responsible for maintaining this pseudonymisation on any data sent to the CTRU. Any exceptions (e.g. collecting unredacted consent forms at the CTRU for central monitoring of informed consent) will only be for legitimate reasons and will be explained fully to participants in advance of data processing. Where central monitoring of source documents, or copies of source documents, is required

by CTRU, the participant's name must be obliterated by site before sending. Any breach of confidentiality or of participants' personal data will be handled and reported (if required) in line with relevant laws.

Data will be made available for secondary research once the main trial objectives are complete.

If a participant withdraws consent from further trial treatment and/or further collection of data, their data will remain on file and will be included in the final trial analysis.

18.1 ARCHIVING

18.1.1 TRIAL DATA AND DOCUMENTS HELD BY CTRU

Trial data will be retained for a minimum of 15 years. When there is no longer a lawful basis for retaining the data, it will be securely destroyed.

18.1.2 TRIAL DATA AND DOCUMENTS HELD BY RESEARCH SITES

Research sites are responsible for archiving all trial data and documents (ISF and all essential documents therein, including CRFs) at the participating research site until authorisation is issued from the Sponsor for confidential destruction.

18.1.3 PARTICIPANT MEDICAL RECORDS HELD BY RESEARCH SITES

Research sites are responsible for archiving trial participant medical records in accordance with the site's policy and procedures for archiving medical records of patients who have participated in a clinical trial. However, participant medical records must be retained until authorisation is received from the Sponsor for confidential destruction of trial documentation.

19 STATEMENT OF INDEMNITY

The Sheffield Teaching Hospitals NHS Trust is able to provide indemnification for liabilities and prospective liabilities arising from negligent harm. Clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

20 TRIAL ORGANISATIONAL STRUCTURE

Research sites will liaise with the CTRU for advice and support on trial set-up and operation, and submission of trial data. In turn, the CTRU will be responsible for data chasing.

20.1 OPERATIONAL STRUCTURE

Chief Investigator (CI): As defined by the NHS UK Policy Framework for Health and Social Care, the CI is responsible for the design, management and reporting of the trial.

Trial Sponsor- Sheffield Teaching Hospitals NHS Trust: The sponsor is responsible for trial initiation management and financing of the trial as defined by the Directive 2001/20/EC. The sponsor delegates some of these responsibilities to CTRU as detailed in the trial contract.

Clinical Trials Research Unit (CTRU): the CTRU at the University of Leeds will have responsibility for the conduct of the trial in accordance with the NHS UK Policy Framework for Health and Social Care and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs and the NHS UK Policy Framework for Health and Social Care including randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, ongoing management including training, monitoring reports and trial promotion, monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support ethical approval submissions, any other site-specific approvals, and clinical set-up. The CTRU will be responsible for the overall day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting, and all statistical analyses. At the end of the trial, CTRU will be responsible for archiving all data and trial data held by the CTRU in line with the Sponsor's procedures for a minimum of 15 years.

Research Sites (local PI): The responsibility for ensuring clinical management of participants is conducted in accordance with the trial protocol ultimately remains with the PI at each research site.

20.2 OVERSIGHT/TRIAL MONITORING GROUPS

Trial Management Group (TMG): the TMG, comprising the CI, CTRU team, other key external members of staff involved in the trial, and a patient representative will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results. Specifically the TMG will be responsible for:

- Protocol completion
- CRF development
- Obtaining approval from the HRA, UK REC and supporting applications for locally required approvals
- Completing cost estimates and project initiation

- Nominating members and facilitating the TSC and DMEC
- Reporting of complications
- Monitoring of screening, recruitment, treatment and follow-up procedures
- Auditing consent procedures, data collection, trial end-point validation and database development.

Trial Steering Committee (TSC): the TSC will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two other independent members, and a consumer representative. The CI and other members of the TMG may attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum and will consider recommendations made by the DMEC.

Data Monitoring and Ethics Committee (DMEC): the DMEC will include independent membership and will review the safety and ethics of the trial by reviewing interim data during recruitment and follow-up. The DMEC meeting will be conducted according to an agreed DMEC Charter and members will be provided with reports prepared by CTRU. The DMEC meeting will consist of open and closed sessions to discuss aggregate data and, in the closed session, data presented by randomised group. The Committee will meet annually as a minimum.

20.3 FUNDING

This project is funded by the National Institute for Health Research. (NIHR) Efficacy and Mechanism Evaluation (EME) Programme (Grant Ref: 17/11/27)

21 PUBLICATION POLICY

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Authorship decisions will be guided by standard requirements for authorship relating to submission of manuscripts to medical journals. These state that authorship credit should be based only on the following conditions being met (http://www.icmje.org):

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data

- Substantial contribution to drafting the article or revising it critically for important intellectual content
- Substantial contribution to final approval of the version to be published.

In light of this, the CI, other grant co-applicants, and relevant senior CTRU staff will be named as authors in any publication, subject to journal authorship restrictions. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial. Where possible publications will also acknowledge the 'NIFTy Group' which will include the PIs and APIs from participating sites.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

On completion of the research project a draft final report will be submitted to the EME programme (trial funder) by the CTRU, within 14 days. This will be peer reviewed and then published on the EME website. The CTRU is obliged to provide NIHR/EME with advanced notice of any publication relating to the trial. Copies of any materials intended for publication will be provided to NIHR/EME at least 28 days prior to submission for publication.

22 ABBREVIATIONS USED

ACRONYM	DEFINITION
ALT	Alanine Transaminase
API	Associate Principal Investigator
APL	Authorised Personnel Log
ASA	American Society of Anesthesiologists
AST	Aminotransferase
BAETS	British Association of Endocrine and Thyroid Surgeons
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigation Medicinal Product
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
eCRF	electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EME	Efficacy and Mechanism Evaluation
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
HSS	Hypocalcaemia Symptoms Score
ICF	Informed Consent Form
ICG	Indocyanine Green
ICMJE	International Committee of Medical Journal Editors
ISF	Investigator Site File
LFT	Liver Function Test
NHS	National Health Service
NIHR	National Institute of Health Research
NIRF	Near Infrared Fluorescence

PI	Principal Investigator
PIN	Personal Identification Number
PIS	Patient Information Sheet
PoSH	Post-surgical hypoparathyroidism
QoL	Quality of Life
RDE	Remote Data Entry
REC	Research Ethics Committee
SC	Serious Complication
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSOP	Site Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
TSH	Thyroid Stimulating Hormone
U&E	Urea & Electrolytes
USC	Unexpected Serious Complication

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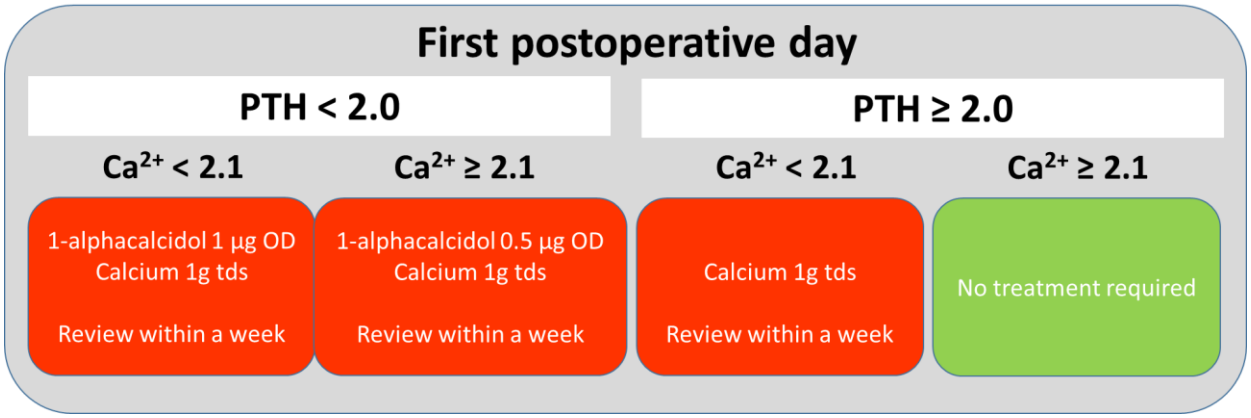
Appendix 1: Protocol for assessment and treatment of post-surgical hypocalcaemia and hypoparathyroidism for patients enrolled in the NIFTy trial

Preoperative management

1. All patients should have a calcium profile which should include as a minimum – serum adjusted calcium, serum PTH, vitamin D and renal function.
2. Patients with vitamin D deficiency (<30 nmol/L) should be treated with high dose vitamin D as per local protocols and continued on maintenance cholecalciferol supplements (of 800 – 1000 IU per day).
3. Patients should not be started on routine (or prophylactic) calcium or active vitamin D supplements.

Early postoperative (prior to discharge) management

1. Patients should not be started on routine (or prophylactic) calcium or active vitamin D supplements
2. Treatment for post-surgical hypocalcaemia should be based on calcium and PTH values on the first postoperative day, as per the following protocol.



Note:

1. For symptomatic (tingling, numbness and/or paresthesia around mouth and tips of fingers and/or toes) patients, take blood for calcium and PTH and give a glass of MILK or 1-2 g calcium supplements and follow above protocol. If both PTH and calcium are fine, you may consider calcium 1 g tds or PRN until clinic review.

Postoperative management after discharge

1. Symptoms and calcium profile should be checked within a week of surgery for patients needing treatment and the dose of medications adjusted as appropriate.
2. Further checks should be carried out every 3-4 weeks until patients have been weaned off any calcium or active vitamin D supplements or for 6 months; whichever is earlier.
3. Management beyond 6 months should be at per the local protocols.
4. General principles of management in this period (post discharge to 6 months)
    a. Aim to keep patients asymptomatic.
    b. In asymptomatic patients, aim to wean patients off supplements gradually if the adjusted calcium remains over 2.0 mmol/L and PTH is stable or improving.
    c. Continue cholecalciferol supplements (1000 IU/day), especially while on treatment with calcium and/or active vitamin D supplements.

Note: For patients not needing treatment on the first postoperative day, a further calcium profile should be done 3-4 weeks after surgery.

APPENDIX 2: Clavien-Dindo Classification of Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III Grade IIIa Grade IIIb	Requiring surgical, endoscopic or radiological intervention Intervention not under general anesthesia Intervention under general anesthesia
Grade IV: Grade IVa Grade IVb	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management Single organ dysfunction (including dialysis) Multi organ dysfunction
Suffix “d”	If the patients suffers from a complication at the time of discharge, the suffix “d” (for ‘disability’) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

‡ brain haemorrhage, ischemic stroke, sub-arachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit.