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HoT Trial

Hemithyroidectomy or Total-Thyroidectomy in 'low-risk' thyroid cancers

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Please note: This trial protocol must not be applied to patients outside the HoT trial. Cancer Research UK & UCL Cancer Trials Centre (UCL CTC) can only ensure that approved trial investigators are provided with amendments to the protocol.

We would like to acknowledge the members of the Butterfly Thyroid Cancer Trust and Welsh Thyroid Cancer Support Group who contributed to the set-up of this trial.

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ABBREVIATIONS

ATA	American Thyroid Association
AUC	Area Under the Curve
BAETS	British Association of Endocrine and Thyroid Surgeons
BTA	British Thyroid Association
CI	Chief Investigator
eCRF	Electronic Case Report Form
DTC	Differentiated Thyroid Cancer
FTC	Follicular Thyroid Carcinoma
FNAC	Fine-needle aspiration cytology
GDPR	General Data Protection Regulation
HES	Hospital Episode Statistics
HRA	Health Research Authority
HT	Hemithyroidectomy
GCP	Good Clinical Practice
IDMC	Independent Data Monitoring Committee
ISF	Investigator Site File
MDT	Multi-Disciplinary Team
NCRI	National Cancer Research Institute
NHS	National Health Service
OS	Overall Survival
PI	Principal Investigator
QOL	Quality of Life
RAI	Radioactive Iodine
REC	Research Ethics Committee
RLN	Recurrent Laryngeal Nerve
Tg	Thyroglobulin
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSH	Thyroid Stimulating Hormone
TT	Total Thyroidectomy
UCL CTC	CR UK and UCL Cancer Trials Centre
US	Ultrasound
UK	United Kingdom
VHI	Voice Handicap Index

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1 PROTOCOL SUMMARY

1.1 Summary of Trial Design

Title:	Hemithyroidectomy or Total-Thyroidectomy in 'low-risk' thyroid cancers
Short Title/acronym:	HoT
Sponsor name & reference:	University College London (UCL/136591)
Funder name & reference:	NIHR128699
ISRCTN:	ISRCTN17004671
Design:	Multi-centre randomised non-inferiority phase III clinical trial
Overall aim:	Pilot phase: to examine feasibility of recruitment Main trial: to compare thyroid cancer recurrence, quality of life, surgical morbidities/effects, and cost-effectiveness between total thyroidectomy and hemithyroidectomy (HT) in a national cancer setting
Primary endpoint:	Pilot phase: monthly patient accrual rates Main trial: 3 year recurrence rate
Secondary endpoints:	• 5 year recurrence rate • Risk of loco-regional recurrence • Anatomical site of recurrence • Number and type of additional investigations and procedures after 1st surgery • Surgical outcomes & complications (RLN & Calcium) • Requirement for hormone replacement therapy • Quality of life • Full cost-effective analysis • Biochemical recurrence (role of Thyroglobulin (Tg) & rising Tg levels after HT)
Exploratory endpoints	Rate of rising thyroglobulin in patients who have HT and those who have non-ablation TT

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Endpoints associated with nested sub-study on OpenClinica ePRO software:	• Percentage of patients who complete the questionnaire, at each of baseline, 2-4 weeks post-surgery, and the 6 month and annual visits • Percentage of questions completed (per patient) for each questionnaire • Timeliness of questionnaire completion via timestamp of form completion relative to the due date
Target accrual:	456 patients
Inclusion & exclusion criteria:	**Inclusion criteria for Group 1 (HT performed prior to diagnosis):** • Low-risk thyroid cancer as defined by the American Thyroid Association 2015 and 8th AJCC TNM staging criteria: • Aged 16 or over *Papillary thyroid cancer:* • pT1b-2 (≤4cm) irrespective of molecular genetic markers • R0 resection (clinically excised but microscopic R1 resected tumours at discretion of the local MDT) • cN0 or pN0, pNX & pN1a (≤5 foci, no extranodal spread) • Confined to thyroid or minimal extrathyroidal extension • No higher risk histological variants on morphology (small foci allowed at the discretion of the local MDT) • No angioinvasion *NB. PTC is still eligible where microscopic invasion of endothelial lined small capillary vascular spaces and lymphatic channels are present. It becomes ineligible in the rare instances when there is definite invasion of a larger vascular structure such as a vein with smooth muscle in its wall.* • Encapsulated FVPTC with capsular invasion only • Micro-PTC (≤1cm) - multifocal - unifocal with pN1a (≤5 foci; no extranodal spread) *Follicular thyroid cancer (FTC), including oncocytic (Hürthle cell) carcinoma:* • pT1b-2 (≤4cm) irrespective of molecular genetic markers - Minimally invasive, with capsular invasion +/- minimal (≤4 foci) vascular invasion • Confined to thyroid or minimal extrathyroidal extension **Exclusion criteria for Group 1 (HT performed prior to diagnosis):** • >4cm • unifocal pT1a (≤1cm) PTC or FTC (unless pN1a as above)

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	• NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features)
	• Anaplastic, poorly differentiated or medullary thyroid carcinoma
	• R2
	• gross extrathyroidal extension
	• pT4 or macroscopic tumour invasion of loco-regional tissues or structures
	• pN1a with >5 foci or extranodal spread
	• pN1b
	• M1
	• Aggressive PTC with any of the following features:
	  - Widely invasive
	  - Poorly differentiated
	  - Anaplastic
	  - predominance of Tall cell, Columnar cell, Hobnail, Diffuse sclerosing and other higher risk variants
	• FTC, including oncocytic (*Hürthle cell)* cancer with any of the following features:
	  - Minimally invasive with extensive vascular invasion (now called encapsulated angioinvasive) (>4 foci)
	  - Widely invasive
	  - Poorly differentiated
	  - Anaplastic
	
	Inclusion criteria for Group 2 (DTC on cytology or after core biopsy with no prior surgery yet):
	• Aged 16 or over
	• 'low risk' differentiated thyroid cancer confirmed by cytology or core biopsy.
	• cT1b-2 irrespective of molecular genetic markers
	• cN0
	• Contralateral lobe without suspicious nodule(s) (U2, or U3/U4 with Thy2 on FNAC)
	
	Exclusion criteria for Group 2 (DTC on cytology or after core biopsy with no prior surgery yet):
	• M1

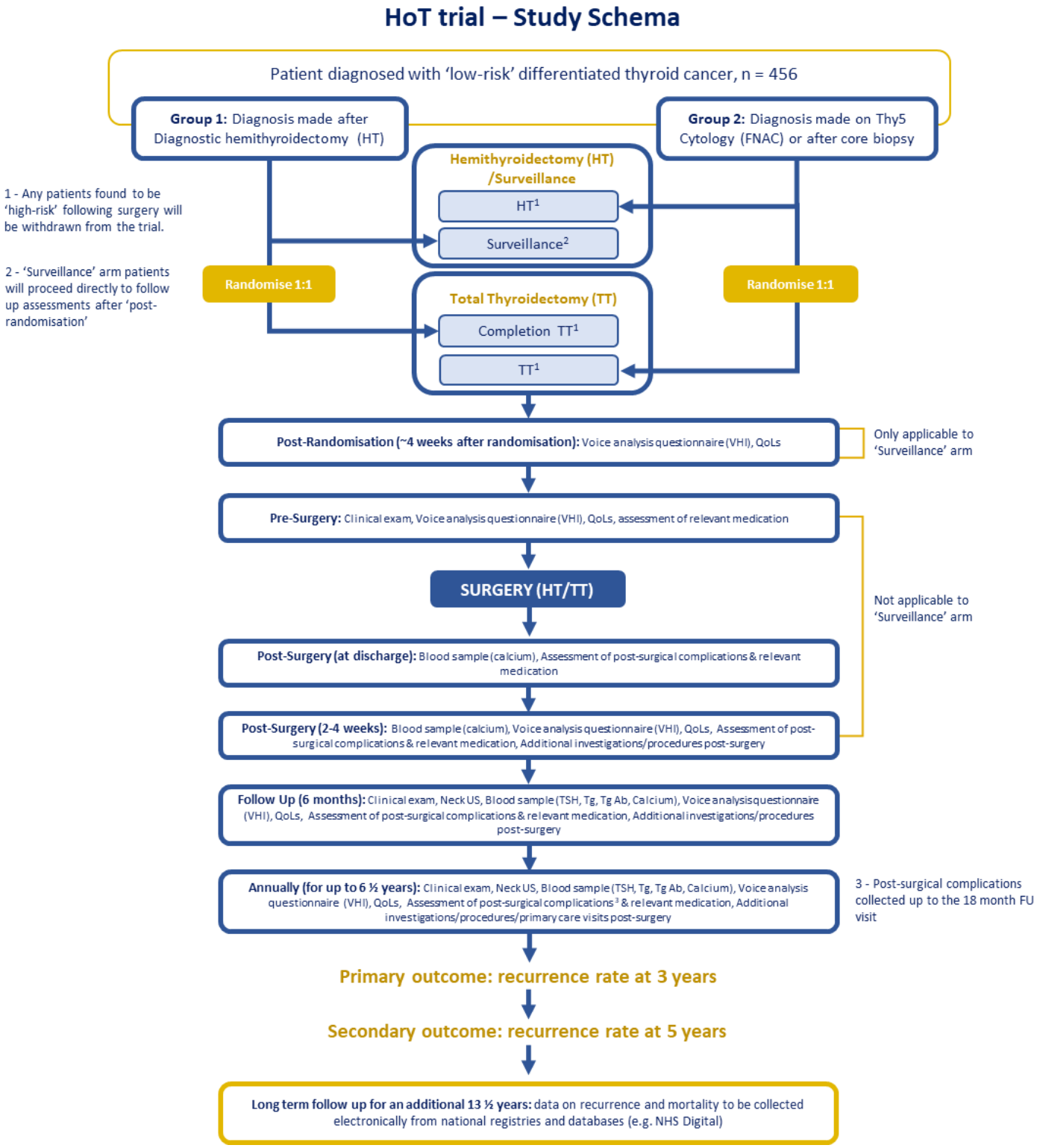
Planned number of sites:	~30

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Treatment summary:	Two groups of patients will be recruited via thyroid MDT meetings: **Group 1:** Patients that have already had a HT for thyroid problems and are then subsequently diagnosed with low risk DTC. Patients will be randomised to: • surveillance only or • a second operation to remove the rest of the thyroid gland (two-stage TT). **Group 2:** Patients that have been diagnosed with 'low risk' DTC using cytology (Thy5) or core biopsy but no surgery performed yet. Patients will be randomised to: • HT or • TT (single stage)
Duration of recruitment:	Estimated 79 months
Duration of follow-up:	Patients will be followed up 6 months after surgery and then annually for up to 6 ½ years.
Definition of end of trial:	20 years after the surgery date of the first patient randomised on to the trial (last patient will be followed up for a minimum of 2 ½ years)
Other related research:	Sub-study conducted by UCL CTC to test the clinical utility of patients completing QoL forms on an electronic patient-reported outcome (ePRO) software versus the traditional method of paper forms.

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1.2 Trial Schema



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2 INTRODUCTION

2.1 Background

The incidence of thyroid cancer is about 3500 cases per year in the UK. The 2016-17 NHS Hospital Episode Statistics (HES) data reported 6400 separate admissions for surgery for thyroid cancer. The incidence of well-differentiated thyroid cancer (DTC) is increasing faster than any other tumour and estimated to increase by 30% by 2022. It is projected to replace colorectal cancer as the fourth leading cancer diagnosis in the US by 2030 (4). Adequate surgery is the most important prognostic determinant in the management of DTC (9). The current standard of care is total thyroidectomy (TT) which involves removing the whole thyroid gland, then post-operative RAI ablation for DTC tumour size >1cm (6). These patients have an excellent prognosis: 10-year overall survival is 98-99%, and recurrence rate 7% by 8 years (7). The vast majority of DTC patients do not die from thyroid cancer, but nevertheless worry about it.

In recent years, some surgeons have started to use hemithyroidectomy (HT) which is removal of half of the thyroid gland (occasionally called lobectomy). A major issue with the current evidence base for HT is that there are only observational studies comparing HT with TT. Nearly all are retrospective reviews of patient records and often from single centres with established expertise in thyroid surgery, and high throughput of patients. These studies will therefore be affected by bias and confounding, and unlikely to be representative of a typical patient population.

In the absence of any randomised trial comparing HT with TT, differential interpretation and implementation of international guidelines by local clinical teams have resulted in variable practices across the UK (National Clinician Survey (1)). There is concern that HT is being adopted sporadically in the absence of high level evidence, both in the UK and internationally. Practice variability and uncertainty over whether patients should accept HT instead of TT has contributed to significant levels of patient anxiety (National Patient Survey; see PPI section in the application (1)). Recent high profile examples of treatment de-intensification in treating early stage cancers demonstrate the potential for harm (2,3), in the absence of controlled randomised studies. For example, minimally invasive surgery for early stage cervical cancer had been steadily introduced into routine practice internationally, given its benefits (lower surgical morbidity and hospital stay), with the assumption that recurrence-free survival would be unaffected. However, a randomised controlled trial showed convincingly that recurrence-free survival was significantly worse with minimally invasive surgery (3), and international practice has had to reconsider its use.

When developing the HoT trial, we conducted a National Clinician Survey and National Patient Survey through two patient public involvement (PPI) groups, the Butterfly Thyroid Cancer Trust (BTCT) and Welsh Thyroid Cancer Support Group (WTCSG); manuscripts in preparation. There was clear support for the HoT trial, and 47% of 215 patients said they would be willing to accept to be randomised to the study.

HT should be associated with several benefits for patients compared to TT: fewer surgical complications, patients may not need lifelong thyroid hormone tablets nor radioactive iodine (RAI) ablation, and improved quality of life. Also, in patients who have already had a HT before

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their diagnosis of thyroid cancer they would not need a second operation (completion TT) after cancer is confirmed. These benefits would be balanced against the possible higher risk of recurrence with HT, bearing in mind that the majority of thyroid cancer recurrences are successfully treated with surgery and high dose RAI therapy.

Moving towards a treatment de-escalation approach - rationale for HT in low-risk DTC

There has already been a shift towards treatment de-escalation in DTC with the HiLo trial, in which the dose of RAI ablation was reduced (8), and the ongoing IoN trial (ClinicalTrials.gov NCT01398085) aims to avoid ablation completely in the lowest risk patients. In a landmark study of 61,775 low-risk patients with tumours 1–4cm in size from the US National Cancer Data Base, overall survival using TT was not materially higher than HT (9). This has been supported by other retrospective studies but with a slightly higher recurrence rate after HT (10-15). Proponents of HT propose that it may benefit patients by reducing the potential sequelae of surgery compared to the more extensive TT including recurrent laryngeal nerve injury, hypocalcaemia and the need for life-long thyroxine therapy. In recognition of this, the American Thyroid Association (ATA) (2015) and British Thyroid Association (BTA) (2015) suggest that HT may be adequate treatment for carefully selected DTC patients with tumour size ≤4 cm (16). However, they acknowledge the lack of any randomised controlled trials.

Surgical equipoise for managing low-risk thyroid cancer patients

Recent studies provide evidence against HT. Hwangbo et al 2017 (17) reported a large multi-centre study in DTC (3282 patients) and observed significantly higher recurrence rates after HT compared to TT (hazard ratio 4.3, $p<0.001$, adjusted for age, tumour size and number of metastatic lymph nodes). Rajjoub et al. 2018 (18) reported that HT was associated with worse overall survival in patients with papillary thyroid cancers (PTC) >2cm (HR 1.53; CI 1.06–2.19, P = .023) after allowing for histology. A meta-analysis by Guo et al (2014) indicated that recurrence at 10 years was significantly higher in DTC patients with size >2cm after HT compared to TT (24% vs 10%) (19).

Recently, we completed a systematic review of outcomes after HT for DTC which highlighted the marked heterogeneity and potential bias in the studies (20). When examining only studies of low-risk DTC, TT was associated with a lower recurrence rate at 10 years than HT (TT 5.7% vs HT 8.5%) but this difference is considered clinically small, and overall survival was similar. Two large cohort studies of low-risk DTC observed higher recurrence rates after HT compared to TT (22.2% vs 8.3% and 18.4% vs 8% respectively) (21,22).

Surgical complications from TT vs HT

Proponents of HT argue that the higher rate of complications after TT outweighs the potentially lower risk of recurrence in low-risk disease given that so few patients experience a recurrence (9,23,24). However, complication rates are known to be dependent on several other factors including, surgical volume of surgeons, method of detection, and between benign and cancer cases (23,25). A Cochrane Systematic Review comparing surgical outcomes after HT vs TT revealed negligible differences in complication rates (recurrent laryngeal nerve palsy: HT = 0.8% vs TT = 0.7%; and hypocalcaemia: HT= 0.1% vs TT = 0.6%) (26). Therefore, just as uncertainty exists surrounding the difference in recurrence risk between TT and HT, the same is true for surgical complications rates.

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Requirement for life-long thyroxine replacement

Another major potential advantage of HT over TT is the reduced requirement for life-long thyroxine replacement treatment (27). Recent work suggested that as many as 72% of patients who undergo HT for low-risk differentiated thyroid cancer may still require additional thyroxine supplements in order to maintain optimal TSH levels, reducing the extent of benefit when experts assert that most patients can avoid thyroxine replacement (28). But even with this high estimate, it still means that a significant 28% of patients can avoid thyroxine supplements completely.

Patient anxiety

Two-thirds of DTC cases are women, and unlike many other cancers, thyroid cancer commonly occurs in younger people (<60 years) therefore many patients have dependent children and are in work. Despite excellent survival outcomes, it is understandable that these patients with DTC fear having a future recurrence (30,31). The existing clinical equipoise and resulting practice variation identified from our National Patient Survey show high levels of confusion, dissatisfaction and anxiety with regards treatment decision and worry during surveillance/follow-up after HT (report by the Butterfly Thyroid Cancer Trust and the national patient survey (manuscript in preparation (1)). The difference in Quality of Life (QoL) during survivorship after HT versus TT in thyroid cancer patients has never been studied and requires evaluation to help treatment decision making (32,33).

Long-term surveillance concerns & cost effectiveness

Employing simulation-based analyses, the survival difference costs between HT and TT have been shown to be comparable. These depend heavily on treatment complication rates, recurrence of disease, additional costs incurred during long-term surveillance (34-36). There is uncertainty over the relative cost-effectiveness of TT (thyroglobulin blood levels and clinical review) vs HT (more expensive serial ultrasound (US) scanning and more fine needle aspiration cytology (FNAC)) (37). This is further justification for a prospective multi-centre randomised trial.

Why this research is needed now?

Differing interpretation of the guidelines has resulted in significant variability in clinical practice in the UK and worldwide. The European Thyroid Association do not support HT generally, particularly for >2cm DTC, and request multicentre randomised trials (29). In conjunction with the UK NCRI and British Association of Endocrine & Thyroid Surgeons (BAETS), we performed a national clinician survey of 74 thyroid surgeons from 53 centres to explore attitudes and practices for low-risk DTC; manuscript in preparation (1). The findings showed that as a direct result of the ATA and BTA guideline changes in 2015, there is now highly variable use of HT within the UK.

The issue of optimal extent of thyroid resection for low-risk DTC is one of the most controversial issues of concern among endocrinologists, surgeons and patients. Although overall survival is likely to be comparable between HT and TT because so few patients die from thyroid cancer, the recurrence rate and need for subsequent surgery might be higher after HT. The current evidence base consists only of observational studies, mostly retrospective reviews of patient records, with design limitations. Studies showing good

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outcomes for HT tend to come from large centres of excellence which are not representative of the majority of cancer centres.

The proposed HoT trial is part of a programme of research aimed at reducing unnecessary treatment of DTC patients who have a very small chance of their cancer coming back. The ultimate goal of HoT is to determine whether HT is an acceptable and cost-effective surgical procedure compared to TT in low risk thyroid cancer. If HT is shown to be non-inferior to TT (with regards cancer recurrence), national and international guidelines will change to recommend HT routinely. If non-inferiority is not shown, the guidelines will still change, but to keep TT as the standard of care, and HT in certain circumstances only.

2.2 Rationale for nested sub-study using electronic patient-reported outcome (ePRO) software

A nested sub-study within the HoT trial represents an opportunity to test the clinical utility of patients completing QoL forms on an electronic patient-reported outcome (ePRO) software versus the traditional method of paper forms. Patient-reported outcomes (PROs, including health-related quality of life (HR-QoL)) are an essential feature of most clinical trials. In many cancer trials, patients complete questionnaires while they are waiting in clinic for their routine assessment. However, there is the problem of missing data due to no form at all (up to 30% of patients) or incomplete forms, because patients do not have the time to complete them during their clinic visit. Investigators have been finding ways to minimise the significant issue of missing data. One such way is making use of people's mobile telephones. This has the advantages of notifying patients when they need to complete a HR-QoL questionnaire, and that this can be done at home in their own time and on time. There is already evidence of the value of using mobile phones in this way but in small studies (38).

The sub-study will be conducted by UCL CTC which will use an ePRO software called OpenClinica Participate.

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3 TRIAL DESIGN

This is a multi-centre randomised non-inferiority phase III clinical trial. It will compare hemithyroidectomy (HT) with total thyroidectomy (TT) and aims to provide definitive evidence as to the most appropriate and cost-effective surgical approach for patients with low-risk DTC.

Eligible patients will be identified via thyroid oncology multidisciplinary team meetings. As it is not always possible to reach a definitive cancer diagnosis preoperatively there will be two sources of patients into the trial, with the same histological diagnoses and prognosis (i.e. recurrence risk):

Group 1: Patients that have already had a HT for thyroid problems and are then subsequently diagnosed with low risk DTC. Patients will be randomised to:

- surveillance only

  or

- a second operation to remove the rest of the thyroid gland (two-stage TT)

Group 2: Patients that have been diagnosed with low risk DTC using cytology (Thy5) or after core biopsy but no surgery performed yet. Patients will be randomised to:

- HT

  or

- TT (single-stage)

As part of the HoT trial, UCL CTC will conduct a sub-study, carried out in two phases to evaluate the utility of an ePRO software for the collection of PRO data in a clinical trial context.

First phase (now closed):

Initially, the sub-study utilised a web-based app designed by a US-based company called Navio. There was an observational phase, where the first 30-50 patients recruited to the HoT trial and who consented to using the Navio app, completed the questionnaires directly in the app using their mobile phone/tablet. Patients who choose not to participate in the sub-study will complete paper QoL/VHI (Voice Handicap Index) forms instead. QoL/VHI data obtained at baseline, 2-4 weeks post-surgery and the 6-month visit will be examined. Variables such as time taken to complete the QoL/VHI questions, number of missing data items, number of missing whole forms, and any software issues will be analysed by UCL as per the objectives and endpoints in sections 3.1 and 3.2 and this may prompt a revision of the assumptions used for the design in the second phase.

Second phase:

Up to 406 patients (the remainder of the target sample size for the main trial) will be asked to consent to use ePRO (on OpenClinica Participate), and those who do will be randomised to either complete electronic or paper QoL/VHI questionnaires (control arm) in clinic. The main research hypothesis is that the completion rate of PROs when using electronic QoL (at home)

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is non-inferior to completing PROs on paper at clinic visits (with the clear benefit that patients do not have to wait around in clinics to complete these).

3.1 Trial Objectives

Primary objective

- Pilot phase: to determine whether the patient accrual rate is high enough for the trial to continue and meet the recruitment targets within the proposed timelines.
- Main trial: To determine whether hemithyroidectomy is non-inferior to total thyroidectomy in low risk thyroid cancer, with regards cancer recurrence.

Secondary objectives

- To compare the anatomical site of recurrence between HT and TT
- To compare the surgical morbidities between HT and TT
- To compare quality of life between patients who undergo HT and TT
- To compare the number and type of additional investigations and treatments required between HT and TT
- To compare the impact of HT and TT on costs and quality adjusted life expectancy over the follow-up of the trial and over patient lifetimes

Exploratory Objectives

- To examine the role of thyroglobulin and rising thyroglobulin in the context of patients who have HT and those who have non-ablation TT.

Objectives associated with nested sub-study on OpenClinica ePRO software:

- To compare the percentage of patients who complete the questionnaires, at each of baseline, 2-4 weeks post-surgery, and the 6 month and annual visits between the OpenClinica Participate electronic arm and control arm.
- To compare the percentage of questions completed (per patient) for each questionnaire between the OpenClinica Participate electronic arm and control arm.
- To compare the timeliness of questionnaire completion via timestamp of form completion relative to the due date in the OpenClinica Participate electronic arm and control arm.

3.2 Trial Endpoints

Primary endpoint

- Pilot phase: Monthly accrual rate
- Main trial: 3 year recurrence rate

Secondary endpoint

- 5 year recurrence rate
- Anatomical site of recurrences

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- Risk of loco-regional recurrence
- Number and type of additional investigations and procedures after surgery
- Surgical complications and severity, including voice function
- Requirement for hormone replacement therapy
- Quality of life
- Cost and health resource use

Exploratory endpoints

- Rate of rising thyroglobulin in patients who have HT and those who have non-ablation TT

Endpoints associated with nested sub-study on OpenClinica ePRO software:

- Percentage of patients who complete the questionnaire, at each of baseline, 2-4 weeks post-surgery, and the 6 month and annual visits
- Percentage of questions completed (per patient) for each questionnaire
- Timeliness of questionnaire completion via timestamp of form completion relative to the due date

3.3 Trial Activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Health Research Authority (HRA) approval, including Research Ethics Committee approval
- **'**Adoption' into NIHR portfolio
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

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4 SELECTION OF SITES/SITE INVESTIGATORS

4.1 Site Selection

In this protocol trial 'site' refers to a hospital where trial-related activities are conducted.

Sites must be able to comply with:

- Trial treatment, imaging, clinical care, follow-up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority, and all amendments
- Data collection requirements, including adherence to eCRF submission timelines as per section 11.5 (Timelines for Data Entry)
- Monitoring requirements, as outlined in protocol section 14 (Trial Monitoring and Oversight)

4.1.1 Selection of Principal Investigator(s) and other investigators at sites

Each site must appoint a Principal Investigator (PI), i.e. a health care professional authorised by the site to lead and coordinate the work of the trial on behalf of a site. However, for the specific purposes of this trial, it is encouraged that 2 co-PIs be identified, one surgeon and one oncologist. This is to ensure engagement is maintained from all modalities. Co-investigators must be trained and approved by the PI(s). All PIs and co-investigators must be medical doctors with experience of treating thyroid cancer.

One PI will be named on the IRAS application and should be delegated as the main PI on the delegation log. PI absences should be actioned as follows:

- If the main PI takes a leave of absence of greater than three months and the Co-PI can perform the PI duties they may be named as the new PI.
- If the Co-PI cannot perform the PI duties permanently, a new suitable replacement PI must be identified by the site. UCL CTC must be informed of all changes promptly.
- UCL CTC may terminate recruitment at a site where a suitable replacement PI cannot be identified.

4.1.2 Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). A current, signed copy of the CV for the PIs must be forwarded to UCL CTC upon request.

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4.2 Site Initiation and Activation

4.2.1 Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which the PIs and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site by site visit or via video conference with site**.** Re-initiating sites may be required where there has been a significant delay between initiation and enrolling the first patient.

4.2.2 Required documentation

The following documentation must be submitted by the site to UCL CTC prior to a site being activated by the UCL CTC trial team:

- Site Registration Form (identifying relevant local staff)
- Surgical audit questionnaire
- Relevant institutional approvals
- A completed site delegation log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- A signed and dated copy of the PI's current CV
- In addition, a signed site agreement between the Sponsor and the relevant institution (usually an NHS Trust/Health Board) must be in place prior to site activation.

4.2.3 Site activation

Once the UCL CTC trial team has received all required documentation and the site has been initiated, notification of site activation will be issued to the PIs, at which point the site may start to approach patients.

Following site activation, the PIs are responsible for ensuring:

- adherence to the most recent version of the protocol
- all relevant site staff are trained in the protocol requirements
- appropriate recruitment and medical care of patients in the trial
- timely completion and return of CRFs (including assessment of all adverse events)
- prompt notification and assessment of all serious adverse events
- that the site has facilities to provide **24 hour medical advice** for trial patients

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5 INFORMED CONSENT

Sites are responsible for assessing a patient's capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheet (PIS), are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form.

Sites must assess a patient's ability to understand verbal and written information in English and whether or not an independent interpreter/NHS approved translator would be required to ensure fully informed consent. If a patient requires an interpreter and none are available, the patient should not be considered for the trial.

Patients must only be considered and offered to consent to the web-based app for quality of life form completion if they are able to read and comprehend the questions. If this is not possible they will not be eligible for the sub-study and must complete the paper forms with the aid of an interpreter at site, if necessary.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions, the current approved patient information sheet for the trial should be discussed with the patient.

It is recommended at least 24 hours is allowed for the patient to consider and discuss participation in the trial. However, in order to avoid unnecessary return visits patients may consent on the same day as being given the information sheet, provided the member of staff taking consent is satisfied that the patient understands the trial and implications. A member of the research team at the hospital must then phone the patient in the following days to confirm that they are still willing to participate in the trial.

Sites may email/post the PIS to patients ahead of their appointment to allow for additional time to consider taking part in the trial. Further guidance on this will be provided at the Site Initiation Visit.

Written informed consent on the current approved version of the consent form for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient medical notes.

Site staff are responsible for:

- checking that the current approved version of the PIS and informed consent form (ICF) are used
- checking that information on the ICF is complete and legible
- checking that the patient has completed and initialled all relevant sections and signed and dated the form
- checking that an appropriate member of staff has countersigned and dated the ICF to confirm that they provided information to the patient
- checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.)

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- following randomisation, adding the patients' trial number to all copies of the ICF, which should be filed in the patient's medical notes and investigator site file (ISF)
- following randomisation, giving the patient a copy of their signed ICF and PIS.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Also refer to section 15 (Withdrawal of Patients).

The option of remote consent will also be available to sites if it is not possible for consent to be taken in person. All steps performed need to be documented clearly and filed in patient notes accordingly.

- The current approved patient information sheet and informed consent form should be provided to the participant to review, via email or post.
- The PI or, where delegated by the PI, other appropriately trained site staff, must have a verbal conversation with the patient via a phone or video call. The conversation must include a full explanation of the trial, all relevant treatment options and the current approved patient information sheet. The patient must have the opportunity to ask questions and the investigator must assess the patient's comprehension.
- The patient must have adequate time to consider the information. Therefore, the patient must have received the PIS and ICF before the phone or video call with the investigator. The patient should have the documents with them during the phone or video call.
- The investigator should guide the patient through how to agree (or disagree if optional) to each item of the ICF. The investigator should guide the patient through which elements are mandatory for participation and which are optional.
- The investigator must document the entire consent process in the patient's medical notes, including:
    - Patient has confirmed verbally that they are happy to proceed to consent and that a discussion has been held
    - Version numbers of the PIS and ICF used
    - Date the PIS and ICF were emailed or posted to the participant
    - Date of the patient's signature: this is the date of consent.
- The patient should initial, sign and date the ICF. They should email or post the completed ICF back to the investigator.
- Once received, the investigator should sign and date the ICF, and add the patient trial number to the ICF.
- The investigator should provide a fully completed copy of the ICF to the patient, file a copy in the patient's medical notes and file a copy in the ISF (with patient email if applicable).

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6 SELECTION OF PATIENTS

There will be two sources of patients in the trial, who have the same histological or cytological diagnoses and prognosis (i.e. recurrence risk):

Group 1: Patients that have already had a HT for thyroid problems followed by subsequent diagnosis of low risk DTC.

Group 2: Patients that have been diagnosed with low risk DTC using cytology or after core biopsy (Thy5) but no prior surgery performed.

6.1 Screening Log

A screening log must be maintained and appropriately filed at site. Sites should record **all** patients identified with low risk DTC and who are therefore eligible for trial and the reasons why they were not randomised in the trial if this is the case. The log must be sent to UCL CTC when requested.

6.2 Patient Eligibility

Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

Patients' eligibility must be confirmed by an investigator who is suitably qualified and who has been allocated this duty, as documented on the site staff delegation log, prior to randomising the patient. Confirmation of eligibility must be documented in the patients' medical notes.

6.2.1 Group 1 (HT already performed prior to diagnosis)

Inclusion criteria

The inclusion criteria represents those patients who are considered to have low-risk thyroid cancer, as defined by the American Thyroid Association 2015 and 8th AJCC TNM staging criteria. Queries in relation to the eligibility criteria must be addressed with UCL CTC prior to randomisation.

- Aged 16 or over

Papillary thyroid cancer:

- pT1b-2 (≤4cm) irrespective of molecular genetic markers
- R0 resection (clinically excised but microscopic R1 resected tumours at discretion of the local MDT)
- cN0 or pN0, pNX & pN1a (≤5 foci, no extranodal spread)
- Confined to thyroid or minimal extrathyroidal extension

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- No higher risk histological variants on morphology (small foci allowed at the discretion of the local MDT)
- No angioinvasion *NB. PTC is still eligible where microscopic invasion of endothelial lined small capillary vascular spaces and lymphatic channels are present. It becomes ineligible in the rare instances when there is definite invasion of a larger vascular structure such as a vein with smooth muscle in its wall.*
- Encapsulated FVPTC with capsular invasion only
- Micro-PTC (≤1cm)
    - multifocal
    - unifocal with pN1a (≤5 foci; no extranodal spread)

Follicular thyroid cancer (FTC), including oncocytic (Hürthle cell) carcinoma:

- pT1b-2 (≤4cm) irrespective of molecular genetic markers
    - Minimally invasive, with capsular invasion +/- minimal (≤4 foci) vascular invasion (the latter is now called encapsulated angioinvasive and is at the discretion of the MDT)
- Confined to thyroid or minimal extrathyroidal extension

Exclusion criteria

- >4cm
- unifocal pT1a (≤1cm) PTC or FTC (unless pN1a as above)
- NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features)
- Anaplastic, poorly differentiated or medullary thyroid carcinoma
- R2
- gross extrathyroidal extension
- pT4 or macroscopic tumour invasion of loco-regional tissues or structures
- pN1a with >5 foci or extranodal spread
- pN1b
- M1
- Aggressive PTC with any of the following features:
    - Widely invasive
    - Poorly differentiated
    - Anaplastic
    - predominance of Tall cell, Columnar cell, Hobnail, Diffuse sclerosing and other higher risk variants
- FTC, including oncocytic (Hürthle cell) cancer with any of the following features:
    - Minimally invasive with extensive vascular invasion (now called encapsulated angioinvasive) (>4 foci)
    - Widely invasive
    - Poorly differentiated
    - Anaplastic

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6.2.2 Group 2 (DTC on cytology or after core biopsy, who has not had prior thyroid surgery yet)

Inclusion criteria

- Aged 16 or over
- 'low risk' differentiated thyroid cancer confirmed by cytology or core biopsy.
- cT1b-2 irrespective of molecular genetic markers
- cN0
- Contralateral lobe without suspicious nodule(s) (U2, or U3/U4 with Thy2 on FNAC)

Exclusion criteria

- M1

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7 RANDOMISATION PROCEDURES

Patients will be randomised within Group 1 and Group 2 using a minimisation algorithm with a 1:1 ratio, using the following stratification factors:

- age (<55 and ≥55)
- histology (papillary thyroid cancer and all others)
- clinical/pathological stage (cT1 and cT2 or pT1 and pT2)

Patients who consent to using OpenClinica Participate (ePRO software) in the second phase of the sub-study will undergo a second randomisation to either complete electronic or paper QoL/VHI questionnaires. The randomisation will be in a 1:1 ratio, using the following stratification factors:

- age (<55 and ≥55)
- sex (male and female)

7.1 Randomisation

Patient randomisation will be performed via a remote data capture system hosted by UCL CTC, and this must be performed prior to commencement of any trial intervention. Pre-randomisation evaluations should be carried out at sites as detailed in section 9.2 (Pre-randomisation assessments)

Site staff responsible for patient randomisation must request access to the electronic case report forms (eCRFs) database by completing their contact details on the Database User Access Form; they must also be assigned this responsibility on the site staff delegation log. Access to the database will be provided by UCL CTC upon receipt of completed forms. Sites should contact UCL CTC if there are any difficulties in accessing the randomisation database.

Following pre-randomisation evaluations, confirmation of eligibility and consent of a patient at a site, the randomisation form must be completed on the remote data capture system. These will be used to confirm patient eligibility. If further information is required UCL CTC will contact the person requesting randomisation to discuss the patient and request updated forms to be submitted.

Note that patients initials, date of birth and sex are required to randomise a patient. Upon randomisation a trial number and treatment allocation (Prior HT+Surveillance/Prior HT+Completion TT)/No prior surgery+HT/No prior surgery+TT) will be assigned for the patient. The patient's trial number and treatment allocation must be recorded in the patient's medical notes. UCL CTC will email confirmation of the patient's inclusion in the trial, their trial number and treatment allocation to the PI(s), main research contact and treating consultant.

CONTACT DETAILS

HoT Trial Manager: 020 3108 4875
ctc.hot@ucl.ac.uk

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Once a patient has been randomised onto the trial they must be provided with a copy of their signed consent form and patient information sheet. After randomisation onto the trial, the patient's general practitioner (GP) should be informed of the patient's involvement in the trial by the site completing and sending the completed GP letter.

For patients who will be using the OpenClinica Participate (ePRO software) to complete trial questionnaires, a site staff member will need to enter the patient's first name, email address and / or mobile phone number into OpenClinica to trigger a link to be sent to the patient for questionnaire completion. Site staff should refer to the OpenClinica Participate guidance document for further instructions.

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8 TRIAL TREATMENT

8.1 Treatment Summary

A total thyroidectomy involves the removal of the entire thyroid gland whereas a hemithyroidectomy involves removing the half of the thyroid gland containing the tumour.

All eligible patients will be randomised to undergo a total-thyroidectomy (whether this is done as a single or two-stage procedure) OR a hemithyroidectomy (refer to flow chart below).

Group 1: Patients that have already had a HT for thyroid problems and are then subsequently diagnosed with low risk DTC. Patients will be randomised to:

- surveillance only

  or

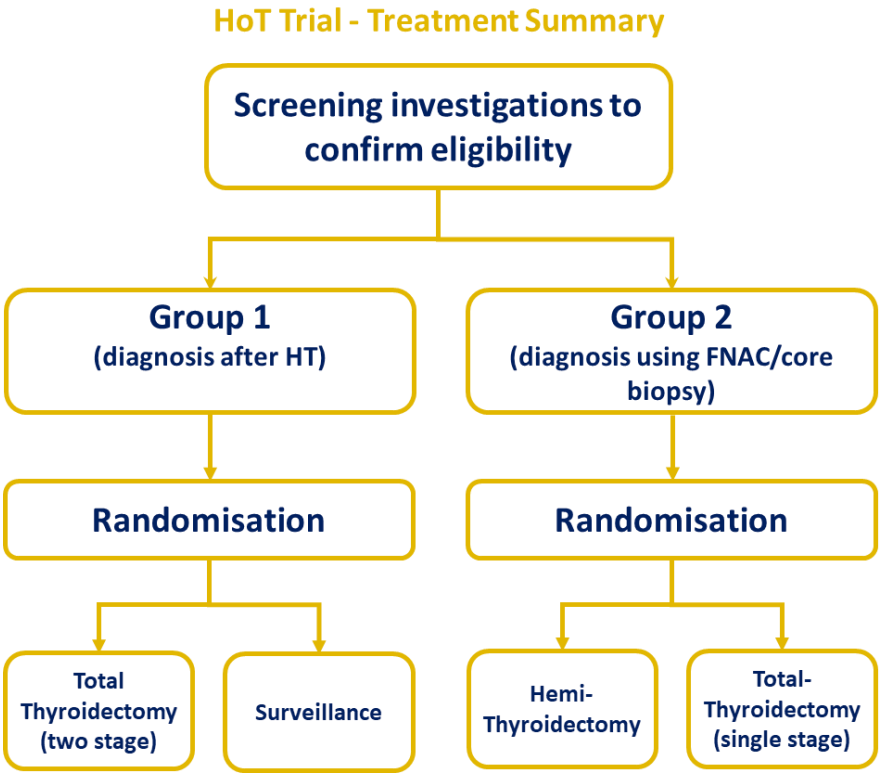
- a second operation to remove the rest of the thyroid gland (two-stage TT).

Group 2: Patients that have been diagnosed with low risk DTC using cytology (Thy5) or after core biopsy but no surgery performed yet. Patients will be randomised to:

- HT

  or

- TT (single stage).



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8.2 Trial Treatment Details

8.2.1 Group 1: Two-stage Completion Thyroidectomy

- Patients will undergo a second operation to remove the remaining lobe of the thyroid (completion thyroidectomy).
- Completion thyroidectomy must take place within 6 months of the hemithyroidectomy performed prior to randomisation.
- Surgery should be performed according to local policy.
- These patients may be treated with RAI post-surgery as per local policy (refer to Section 8.3.1 (Radioiodine ablation) for more details).

8.2.2 Group 1: Surveillance only

- These patients will not have a second surgery, instead will proceed directly to the post-surgery 6 month follow-up visit (timed from their pre-randomisation HT) as outlined in section 9.7 (Assessments during follow-up).
- Pre-trial hemithyroidectomy must be within 6 months of randomisation. (1st FU visit is due 6 month after Pre-trial HT date)

8.2.3 Group 2: Hemithyroidectomy

- Patients will undergo a single operation to remove half of the thyroid gland containing the tumour.
- HT should be performed within 3 months of the randomisation date.
- Surgery should be performed according to local policy.

8.2.4 Group 2: Total-Thyroidectomy

- Patients will undergo a single operation to remove the entire thyroid gland.
- TT should be performed within 3 months of the randomisation date.
- Surgery should be performed according to local policy.
- These patients may be treated with RAI post-surgery as per local policy (refer to Section 8.3.1 (Radioiodine ablation) for more details).

A prophylactic central node dissection could be carried out as part of the surgery if it is local practice at the site. All of the above surgeries are standard of care so the protocol does not mandate any pre-medication or rescue medication, as well as any procedures for patient monitoring or care immediately before and post-surgery. Some guidance on supportive therapy is outlined in section 8.3 (Supportive Therapy). It is expected that all participating sites will monitor and treat patients according to their local policy and the biochemical, physiological, pathological parameters will be fulfilled accordingly for a patient to be treated. Management of post-surgical complications should also be carried out according to local policy.

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8.3 Supportive Therapy

Dynamic risk stratification after TT should be performed as per local standard practice.

8.3.1 Radioiodine ablation

Patients randomised to receive TT (1 or 2 stage) may be treated with radioactive iodine (RAI) after their surgery at the discretion of the treating clinician. RAI treatment is not mandated within the trial and the treating clinician should follow local guidelines.

8.3.2 Management of Hypocalcaemia

In case of hypocalcaemia after surgery investigators should follow local guidelines for clinical management.

8.3.3 TSH Suppression Therapy:

Patients who undergo a total thyroidectomy (1 or 2 stage) will require thyroxine replacement therapy. Patients who are randomised to receive a hemithyroidectomy only may also require thyroxine replacement therapy.

Adequate levothyroxine treatment must be maintained throughout the trial period with the following aims:

- Keep the patient euthyroid
- Maintain TSH low-to-mid normal range (TSH 0.3-2) optimally (BTA Guidelines, 2014) (39).

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9 ASSESSMENTS

9.1 Schedule of Assessments Table

	Pre-randomisation**	Post-randomisation*** *(Only applicable for ' Prior HT+ Surveillance' arm)*	Surgery *(N/A for 'Prior HT+Surveillance' arm)*			Follow-up						
			Pre-surgery	Post-surgery *(prior to discharge)*	Post-Surgery *(2-4 weeks)*	6 months	18 months	30 months	42 months	54 months	66 months	78 months
Screening	X											
Informed consent	X											
Histological/cytological confirmation of DTC	X											
Relevant medical/surgical history	X[a]											
Concomitant Medications (on trial)			X	X	X	X	X	X	X	X	X	X
Clinical examination	X[b]		X			X	X	X	X	X	X	X
WHO Performance Status	X[b]		X			X	X	X	X	X	X	X
Routine bloods (Calcium)				X	X							
Routine bloods (TSH, Tg, Tg antibody, Calcium)						X	X	X	X	X	X	X
Post-surgical complications				X	X	X	X					
Voice analysis questionnaire (VHI-10)		X[c]	X[d]		X	X	X	X	X	X	X	X
Quality of Life questionnaires*		X[c]	X[d]		X	X	X	X	X	X	X	X
Additional investigations/procedures performed after thyroid surgery					X	X	X	X	X	X	X	X
Review of primary care visits						X	X	X	X	X	X	X
Neck ultrasound scan						X	X	X	X	X	X	X
eCRF completion, query resolution	X		X	X	X	X	X	X	X	X	X	X

*QLQ-C30, QLQ-THY34 and EQ-5D-5L, FoP-Q-SF (Fear of Progression)

** After being randomised on the study, consenting patients will be randomised to complete QoL/VHI questionnaires on paper forms Vs electronic forms (OpenClinica Participate)

***Not required for patients with a pre trial HT older than 4 months at randomisation

NOTE: Patients randomised to receive Total Thyroidectomy will receive radioactive iodine (RAI) at the discretion of the treating clinician and is not mandated within this trial.

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a – within 7 days of randomisation
b – within 3 months of randomisation
c – QoL/VHI questionnaires to be completed ~4 weeks after randomisation
d – QoL/VHI questionnaires to be completed after randomisation but prior to surgery

9.2 Pre-randomisation assessments

The following assessments or procedures are required to evaluate the suitability of patients for the trial:

- histological or cytological (FNAC/core biopsy) confirmation of DTC
- TNM staging: 8th edition AJCC
- Informed consent

Within 7 days prior to randomisation:

- Relevant medical and surgical history

Within 3 months prior to randomisation:

- Clinical examination
- WHO performance status

9.3 Post-randomisation assessments to be completed ~4 weeks after randomisation (only applicable for 'Prior HT+Surveillance' arm)

- Voice analysis questionnaire (VHI-10) and QLQ-C30, QLQ-THY34, EQ-5D-5L, FoP-QF-SF (Fear of Progression) quality of life questionnaires to be completed (patients completing electronic QoL will be sent an email / text message to complete the questionnaires at this timepoint)
- Not required for patients with a pre trial HT older than 4 months at randomisation (nearly time for their 6M follow up QoLs)

NB: Surgery related assessment sections, 9.4 (Pre-surgery assessments), 9.5 (Surgery-related data) and 9.6 (Post-surgery assessments) are not applicable to Group 1 patients randomised to the 'Prior HT+Surveillance' arm. These patients will proceed directly to follow-up assessments and must be seen in clinic 6 months after their pre-trial surgery then annually for up to 6 ½ years (as per section 9.7 (Assessments during follow-up)).

9.4 Pre-surgery assessments to be completed after randomisation and prior to surgery (not required for 'Prior HT+Surveillance' arm)

The following assessments should be performed when the patient attends the clinic for their pre-surgery assessments:

- Relevant medication (thyroxine replacement therapy (T3/T4), vitamin D or calcium supplements, anti-coagulant/antiplatelet therapy) taken since randomisation
- Clinical exam

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- WHO Performance Status
- Voice analysis questionnaire (VHI-10) and QLQ-C30, QLQ-THY34, EQ-5D-5L, FoP-QF-SF (Fear of Progression) quality of life questionnaires to be completed (patients completing electronic QoL will be sent an email / text message to complete the questionnaires at this timepoint)

9.5 Surgery related data **(not required for 'Prior HT+Surveillance' arm)**

The following surgery data will be recorded on the Surgery eCRF

- type of surgery
- hospitalisation length

9.6 Post-surgery assessments **(not required for 'Prior HT+Surveillance' arm)**

9.6.1 Assessments to be completed prior to discharge

- Relevant medication (thyroxine replacement therapy, vitamin D or calcium supplements, anti-coagulant/antiplatelet therapy) taken since randomisation
- Blood samples to measure calcium levels as per local practice
- Post-surgical complications experienced since surgery (see section 9.6.3 below)

9.6.2 Assessments to be completed 2-4 weeks Post-Surgery **(not required for 'Prior HT+Surveillance' arm)**

- Relevant medication (thyroxine replacement therapy, vitamin D or calcium supplements, anti-coagulant/antiplatelet therapy) taken since surgery
- Blood samples to measure calcium levels as per local practice
- Post-surgical complications experienced since surgery (see section 9.6.3 below)
- Voice analysis questionnaire (VHI-10) and QLQ-C30, QLQ-THY34, EQ-5D-5L, FoP-Q-SF (Fear of Progression) quality of life questionnaires to be completed (patients completing electronic QoL will be sent an email / text message to complete the questionnaires at this timepoint)
- Information of readmission within 30 days of surgery
- Additional investigations and procedures performed after surgery

9.6.3 Post-surgical complications **(not applicable for 'Prior HT+Surveillance' arm)**

Post-surgical complications should be assessed prior to discharge and at 2-4 weeks post-surgery. Parameters will include the following:

- Recurrent laryngeal nerve palsy/voice change
- Hypocalcaemia (according to BAETS guidelines)
- Wound infection requiring treatment
- Re-operation for bleeding in the neck
- Wound haematoma (not large enough to require re-operation)

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- Seroma
- Chyle leak
- Tracheal injury/fistula
- Oesophageal injury/fistula
- Thyroid storm

The above surgical complications are commonly associated with HT and TT (40).

9.7 Assessments during follow-up

Patients will be followed up 6 months after their surgery then annually for up to 6 ½ years. The final patient registered on the trial will be followed up for 2½ years at the 'end of trial' timepoint. Patients should be followed up according to routine practice.

If it is not possible for the patient to attend the follow-up appointment in person, a telephone/video consultation with the clinician may be carried out. Under such circumstances, sites must ensure the patient still attends for the ultrasound scan and blood tests if it is possible to do so and the questionnaires should be posted to the patient's home.

All efforts should be made by the site to contact the patient's GP to assess their condition, if a patient fails to attend a clinic or cannot be followed up at site.

9.7.1 6 months post-surgery then annually for up to 6 ½ years (+/- 6 weeks)

- Relevant medication (thyroxine replacement therapy, vitamin D or calcium supplements, anti-coagulant/antiplatelet therapy) taken since surgery
- Clinical exam
- WHO Performance Status
- Blood samples as per local practice (including TSH, Tg, Tg antibody, calcium)
- Neck ultrasound
- Post-surgical complications experienced since surgery (see section 9.6.3 for parameters to assess) **(6m and 18m visits only)**
- Voice analysis questionnaire (VHI-10) and QLQ-C30, QLQ-THY34, EQ-5D-5L, FoP-Q-SF (Fear of Progression) quality of life questionnaires to be completed (patients completing electronic QoL will be sent an email / text message to complete the questionnaires at this timepoint)
- Additional investigations and procedures performed after surgery.
- Review of number and type of primary care visits

6 ½ years after the first patient is recruited to the trial, long-term follow-up data on all patients including data on recurrences and mortality will be collected electronically from cancer or other national registries and databases (e.g. NHS digital). The long term follow-up will continue for an additional 13 ½ years and data will only be gathered if the patient does not withdraw consent.

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9.8 Assessments if residual or recurrent disease is suspected

9.8.1 Residual or local recurrence

The most common site for recurrence is loco-regional. Residual or recurrent disease should be suspected only after considering a combination of assessments including:

- Clinical assessment
- Rising thyroglobulin (patients who have had TT)
- Structural imaging e.g ultrasound, +/- MRI or CT

Tissue diagnosis (fine needle aspirate cytology [FNAC] or biopsy) triggered by the above investigations is required to confirm structural loco-regional recurrence or residual disease in HoT (standard practice in the UK). If a site cannot confirm residual or local recurrence with tissue diagnosis a sufficient reason must be provided.

If a recurrence or residual disease is suspected further diagnostic assessments or imaging should be considered according to standard local practice and on a case by case basis.

There is concern about earlier diagnosis of recurrence in the TT+/-RAI ablation arm because of the increased sensitivity and specificity of Tg. Most recurrences are detected in 3-5 years even without routine annual US for five years (11,27,30). However, this ascertainment bias can be counteracted by mandatory requirement of an annual US and tissue diagnosis of structural recurrence or residual disease.

9.8.2 Distant disease recurrence

The most common sites of distant disease recurrence are lung and bone.

If a distance recurrence is suspected further diagnostic assessments (i.e. rising Tg levels) or imaging should be considered according to standard local practice and on a case by case basis. Biopsy is not required, or possible, in most cases.

The ultrasound scans at the 6 month follow-up and annual thereafter will help detect recurrent/residual loco-regional disease without any significant delay. This also applies to patients with Tg antibodies.

9.9 Exploratory analyses of biochemical recurrence

There is some early evidence to support the use of rising Tg levels in non-ablated TT patients to detect recurrent and distant disease. There remains limited evidence for using Tg levels for HT patients. For both HT and No-RAI ablation TT cases, serial rise in Tg may be important (with the same level of TSH suppression). Tg doubling time may also be used both for HT and non-ablated TT cases.

The following biological markers will be measured and monitored in this trial (as per the assessment details outlined above) to help us understand if they can be used as indicators of biochemical recurrence:

- Rising Tg
- Tg doubling time
- Tg antibody

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10 QUALITY ASSURANCE

10.1 Quality Assurance for Surgery

All participating sites must complete and submit an audit of their 20 most recent HT operations and 20 most recent TT (or completion TT) operations (without central level-6 dissection) for outcome data prior to activation.
Post-operative complications will be closely monitored as part of data collection procedures and these will be reviewed regularly by the Trial Management Group and Independent Data Monitoring Committee.

Specific outcomes of interest include:

- Rate of hypocalcaemia (as a result of hypoparathyroidism)
- RLN injury –on nasendoscopy or patient-reported voice change

10.2 Central Histological Review

For quality assurance purposes central histological review will be undertaken for 20% of patients (randomly selected), to confirm low risk status (tumour type and staging). This review will be done retrospectively and not be used to manage patients.

Within one month of request all slides from the HT/TT should be sent for review to the following address:

HoT Trial Manager
Cancer Research UK & UCL Cancer Trials Centre
90 Tottenham Court Road
London
W1T 4TJ

All original stained histology slides should be sent by post and a 'HoT trial histology review submission form' should be included along with a copy of the original pathology report(s). The pathology reports must have all patient identifiers removed and patient trial number and initials added before sending to UCL CTC.

UCL CTC will check slides and documentation, and sites will be contacted if there are any queries.

Selected patients will be reviewed by a central pathologist. Any diagnosis that is different to the site diagnosis will be reviewed by another central reviewer. Slides will be returned to the site once central review is complete.

It is not intended that sites will be informed of the outcome of central histology review, however if there is a significant discrepancy with the original result the CI/TMG will be consulted and where they consider it may be in the patient's best interests the result will be passed to the site investigator.

Documentation required for submission of slides for central review can be found in the Investigator Site File.

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11 DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected from sites using electronic case report forms (eCRFs) on a trial specific OpenClinica database created and maintained by UCL CTC. Data must be accurately transcribed on to trial eCRFs and must be verifiable from source data at site. Examples of source documents are hospital records, which include patient's medical notes, laboratory and other clinical reports etc.

Where copies of supporting source documentation (e.g. pathology reports etc.) are being submitted to UCL CTC, the patient's initials and trial number must be clearly indicated on all material and all patient identifiers removed/blacked out prior to sending, to maintain confidentiality. Refer to section 14 (Trial Monitoring and Oversight) for further details of remote monitoring of source documentation.

Please note that, for this trial, patients must consent to their date of birth and NHS/CHI number being supplied to UCL CTC. These are required to assist with long-term follow-up via national health data registries and databases e.g. NHS Digital. UCL CTC will also collect patient's full postcode in order to carry out sociodemographic analysis and assess participants' background and socioeconomic status.

11.1 Data collection via OpenClinica Participate

In the HoT trial, PROMs data (QoL/VHI data) will be collected via an ePRO software called OpenClinica Participate. Patient consent will be required for the use of the ePRO software, and although this will be the preferred method of collection for PROMs data, patients who do not consent to completing electronic QoL forms, must be given the option of using the paper versions of the forms. If a patient opts out of completing electronic QoL forms at any time during the study they must be asked to complete the paper versions of the forms. Patients who consent to the sub-study evaluating the ePRO software must supply their mobile number or email address to research staff at site who will enter it onto OpenClinica Participate, allowing text/email invitations for completing questionnaires to be sent. This is outlined in more detail in the PIS and consent form. The HoT trial is ideally suited to making use of an ePRO software because many patients are relatively young (<60 years) and they are familiar with these types of apps.

The following questionnaires will need to be completed by patients on OpenClinica Participate via their mobile phone or hand-held tablet:

- EORTC QLQ-C30
- EORTC QLQ-THY34
- EQ-5D-5L
- FoP-Q-SF (Fear of Progression)
- VHI-10 (Voice Handicap Index (VHI) Questionnaire)

Further usage guidance on OpenClinica Participate is to be provided to research staff at local sites in a separate document.

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11.2 Entering data into the eCRF

The eCRF must be completed by site staff who have been appropriately trained, are listed on the site staff delegation log and authorised by the PI to perform this duty. Each authorised staff member will be issued with their own unique login details for the eCRF by UCL CTC, and a list of current users at each site will be maintained by UCL CTC. Site staff must never share their login details with other staff as the eCRF audit trail will record all entries/changes made by each user. The PI(s) is/are responsible for the accuracy of all data reported in the eCRF.

The use of abbreviations and acronyms must be avoided.

11.3 Corrections to eCRF Forms

Where necessary, corrections can be made by site staff to data on the eCRF, as long as the eCRF has not been locked/frozen by UCL CTC. The eCRF audit trail will record the original data, the change made, the user making the change and the date and time. Site staff should contact UCL CTC if changes need to be made to a locked/frozen eCRF.

11.4 Missing Data

To avoid the need for unnecessary data queries, fields should not be left blank on the eCRF. If data is unavailable, please refer to the HoT OpenClinica Site Training Slides for information on how to indicate that data is not available (only use if every effort has been made to obtain the data).

11.5 Timelines for Data Entry

eCRFs must be entered on the remote trial database as soon as possible after the relevant visit and within 1 month of the patient being seen. Eligibility and randomisation forms must be completed for a patient before they are enrolled onto the trial.

Sites who persistently do not enter data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and this may trigger a monitoring visit. See section 14.2 (‘Triggered’ On-Site/Remote Monitoring) for details.

11.6 Data Queries

Data entered onto the eCRF will be subject to some basic checks at the time of entry, and any discrepancies or missing fields will be flagged to the user in the form of an error message. If a Query is not added manually, the system will prompt the user to allow adding an automatic query when the user closes the form. The user must either resolve the error manually (by updating the value or adding a Query) or let the system add an autoquery. Once a Query is added, the error message will be hidden.

Further data review will be carried out at UCL CTC, the eCRF will be checked for completeness, accuracy and consistency, including checks for missing or unusual values and queries raised where necessary. A report listing open queries on the database will be sent to the data contact

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at site. Further guidance on the process for handling data queries can be found in the HoT OpenClinica Site Training Slides.

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12 SAFETY REPORTING

12.1 Definitions

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6.

Adverse Reaction (AR)

All untoward and unintended responses to an investigational treatment. A causal relationship between an investigational treatment and an adverse reaction is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

For the purpose of this trial, all post-surgical complications experienced as a result of having the relevant pre-trial/on-trial thyroid surgery (i.e. all trial arms) need to be reported as ARs. See section 12.2.4 for AR reporting procedures.

Serious Adverse Reaction (SAR)

An Adverse Reaction that:

- Results in death
- Is life threatening (the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

For the purpose of this trial, only post-surgical complications experienced as a result of having the relevant on-trial thyroid surgery (i.e. 'Prior HT+Surveillance' arm excluded) need to be reported as SARs. See section 12.2.5 for SAR reporting procedures.

Related and Unexpected Serious Adverse Reaction (RUSAR)

A serious Adverse Reaction, the nature or severity of which is not consistent with the applicable reference safety information (see list of expected adverse reactions in appendix 1).

i.e. an Adverse Reaction that meets all the following criteria:

- **Serious** – meets one or more of the serious criteria, listed under the definition of SAR above

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- **Related** – assessed by the local PI or designee, or Sponsor as causally related to one or more elements of the trial surgery
- **Unexpected** – the event is not consistent with the applicable reference safety information

See section 12.3 (Reporting of Related and Unexpected Serious Adverse Reactions) for reporting procedures for these events.

12.2 Reporting Procedures

12.2.1 Adverse Reaction Term

An adverse reaction term must be provided for each Adverse Reaction.

- The eCRF will include a list of expected post-surgical adverse reactions commonly associated with total or hemithyroidectomies corresponding to Appendix 1. This list will use the appropriate adverse reaction term from the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
- If the adverse reaction isn't listed in Appendix 1, a valid term from CTCAE v5.0 should be used, wherever possible. This is available online at:

  https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

12.2.2 Severity grade

Severity grade of each adverse reaction must be determined by using CTCAE v5.0, wherever possible.

12.2.3 Sponsor Clinical Review

Only events that are causally related (i.e. Adverse Reactions) need to be reported to UCL CTC. The local PI or designee must check whether the event is causally related to the trial surgery. For SARs a review will also be carried out by the Sponsor's delegate. Initial SAR Reports and significant updates will be sent to the clinical reviewer for sponsor clinical review, to request whether they have:

- any safety concerns
- or any queries for the sites

UCL CTC will consider post-surgical events evaluated as related to the patient's thyroid surgery to be adverse reactions.

12.2.4 Reporting of Adverse Reactions (ARs)

All ARs that occur from the pre-trial/on-trial thyroid surgery to the 18 month follow-up visit must be recorded in the patient medical notes and the trial eCRFs.

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Those meeting the definition of a Serious Adverse Reaction (SAR) must also be reported to UCL CTC using the trial specific SAR Report. Also see section 12.2.5 (Reporting of Serious Adverse Reactions).

12.2.5 Reporting of Serious Adverse Reactions (SARs)

All SARs that occur from the on-trial thyroid surgery to the 18 month follow-up visit must be submitted to UCL CTC by email within 24 hours of observing or learning of the event, using the trial specific SAR Report (NB this excludes patients in the 'Prior HT+Surveillance' arm). All sections on the SAR Report must be completed. If the event is **not being reported to UCL CTC within 24 hours**, the circumstances that led to this must be detailed in the SAR Report to avoid unnecessary queries.

12.2.6 Exemptions from SAR Report submission

For this trial, the following events are exempt from requiring submission on a SAR Report **unless considered to be related to the trial surgery**. However, the events must be recorded in the relevant section(s) of the trial eCRFs:

- events that occur more than **18 months** post-surgery
- disease progression (including disease-related deaths)
- SARs experienced by patients randomised to 'Prior HT+Surveillance' arm

Please note that hospitalisation for elective treatment, palliative care, socio-economic or logistic reasons does not qualify as an SAR.

Completed SAR Reports must be emailed to UCL CTC within 24 hours of becoming aware of the event

Email: ctc.hot@ucl.ac.uk

12.2.7 SAR Follow-Up Reports

UCL CTC will follow up all SARs until resolution and until there are no further queries.

Sites must ensure any new and relevant information is provided to UCL CTC promptly. If an event term changes or a new event is added, the causality must be re-assessed by an Investigator. If the event is not being reported to UCL CTC within 24 hours, the circumstances that led to the delay must be detailed in the SAR Report to avoid unnecessary queries.

12.2.8 SAR Processing at UCL CTC

On receipt of the SAR Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the approved RSI (the list of expected adverse events in protocol appendix 1).

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The CI, or their delegate (e.g. a clinical member of the TMG), will review the SAR and perform a clinical review on behalf of the sponsor. If UCL CTC has considered expectedness difficult to determine, the reviewer will be consulted for their opinion at this time.

12.3 Reporting of Related and Unexpected Serious Adverse Reactions (RUSARs)

If the event is evaluated as a Related and Unexpected Serious Adverse Reaction, UCL CTC will submit a report to the REC within the required timeline. Wherever possible, evaluations of causal relationship by both the site and the Sponsor's clinical reviewer will be reported.

UCL CTC will inform all UK sites of any RUSARs (i.e. related and unexpected SARs) that occur on the trial. Sites will receive a quarterly line listing which must be processed according to local requirements.

12.4 Safety Monitoring

UCL CTC will provide safety information to the Trial Management Group (TMG) and the Independent Data Monitoring Committee (IDMC) on a periodic basis for review.

The IDMC will review the following trial safety data:

- Disease-related events (exempt from SAR reporting as per section 12.2.6) according to treatment allocation to identify whether disease-related events appear to be enhanced by the trial surgery;
- Line listing of adverse reactions to the trial surgery to identify new adverse reactions;

The IDMC and TMG will review trial safety data to identify:

- New adverse reactions to the trial surgery
- the incidence of serious adverse reactions by surgical treatment arm
- Trial related events or incidents that may lead to changes to the trial documents.

If UCL CTC identifies or suspects any issues concerning patient safety at any point during the trial, the CI or TMG will be consulted for their opinion, and if necessary the issue will be referred to the IDMC.

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13 INCIDENT REPORTING AND SERIOUS BREACHES

13.1 Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. When an incident report is requested by UCL CTC this should be provided, but an equivalent document (e.g. Trust incident form) is acceptable where already completed.

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach

13.2 Serious Breaches

A "serious breach" is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

Systematic or persistent non-compliance by a site with the principles and conditions of GCP and/or the protocol, including failure to report SARs occurring on study within the specified timeframe, may be deemed a serious breach.

In cases where a serious breach has been identified, UCL CTC will inform the REC within 7 calendar days of becoming aware of the breach.

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14 TRIAL MONITORING AND OVERSIGHT

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Where permitted by site policy, remote access to source data/documents may also be provided by participating sites for remote monitoring by UCL CTC or its representatives.

Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form. UCL CTC or its representatives will conduct all monitoring in compliance with the participant consent, site policy and Data Protection requirements.

UCL CTC will determine the appropriate level and nature of monitoring required, based on the objective, purpose, phase, design, size, complexity, endpoints and risks associated with the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

Details of monitoring activities will be included in the trial monitoring plan and conveyed to sites during initiation. The trial monitoring plan will be kept under review during the trial and updated information provided to sites as necessary.

14.1 Centralised Monitoring

UCL CTC performs centralised monitoring, which requires the submission of documents by sites to UCL CTC for review, including but not limited to: Site staff delegation log, screening log and PIs current CV (signed & dated). Expectations for document submission will be explained during site initiation and UCL CTC or its representatives will send emails to sites requesting the documents when required.

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File at the frequency determined for the trial. Checklists detailing the current version/date of version-controlled documents will be provided by UCL CTC for this purpose.

14.2 'Triggered' On-Site/Remote Monitoring

On-site or remote monitoring visits may be scheduled following UCL CTC review and/or where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements.

On-site Monitoring

Sites will be sent an email in advance outlining the reason(s) for the visit and confirming when it will take place. The email will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

Remote Monitoring

UCL CTC defines remote monitoring as monitoring activities conducted at a location remote from the research site which replicate some on-site activities e.g. source data review. Remote monitoring may be conducted in response to exceptional circumstances preventing access to

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participating sites (e.g. global pandemic). Details of remote monitoring will be agreed with participating sites, conducted in accordance with site policy and documented in the monitoring plan.

Sites will be sent an email in advance, confirming when remote monitoring is scheduled to take place and how the source documents will be remotely accessed. The email will include a list of the documents to be reviewed, interviews that will be conducted via telephone/videoconference and who will be performing the remote monitoring.

Remote monitoring will be conducted by UCL CTC or its representatives, via a device with adequate security. Patient confidentiality will be maintained at all times, and monitoring activities will be conducted in an appropriate environment where no unauthorised viewing or overhearing of conversations is possible by third parties. Also refer to section 11 (Data Management and Data Handling Guidelines) for details of how source documentation may be submitted to UCL CTC.

Monitoring Follow-up

Following a remote or on-site monitoring visit, the Trial Monitor/Trial Coordinator will provide a follow-up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions required. The PI(s) at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

Where monitoring of data indicates that a patient may have been placed at risk, the matter will be raised urgently with site staff and escalated as appropriate (refer to section 13 (Incident Reporting and Serious Breaches)).

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach. Refer to section 13 (Incident Reporting and Serious Breaches) for details.

14.3 Oversight Committees

14.3.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialties and HoT trial staff from UCL CTC (see pages 2 and 3). The TMG will be responsible for overseeing the trial. The group will meet periodically during the course of the project, approximately every 3 months in the set-up and feasibility recruitment phase of the trial. The TMG will review site set-up progress, recruitment rates and data return and provide advice if any issues are being faced with site set-up and accrual targets. The TMG will provide input into suitable remedial actions and provide other expert advice in clinical and practical aspects of the trial and trial design to support participating hospital sites.

The TMG will review substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individual and are responsible for their prompt implementation.

All non-CTC members will be required to sign the HoT TMG charter and to declare all conflicts of interest.

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14.3.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and the Sponsor.

The HoT trial will be reviewed by an established UCL CTC TSC that has oversight of a number of trials. All members have signed a TSC charter.

14.3.3 Independent Data Monitoring Committee (IDMC)

The IDMC will review trial progress at 6-monthly intervals during the 18 month pilot phase, and will make a recommendation on continuation of the trial beyond the pilot phase which will be reported to the funder.

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. After the pilot phase, meetings of the Committee will be held approximately annually to review recruitment rates, site performance metrics such as data return, recurrence rates, surgical morbidities, and patient issues.

The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC. All IDMC members will sign an IDMC charter prior to their first meeting.

14.3.4 Role of UCL CTC

UCL CTC, on behalf of the sponsor, will be responsible for the day to day coordination and management of the trial and the UCL CTC Director will act as custodian of the data generated in the trial (on behalf of UCL).

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15 WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, assessments, follow-up and data collection.

15.1 Patients who do not undergo trial surgery (after randomisation)

If a patient does not undergo the surgery they were randomised to receive or undergoes a different surgery, reasons for this must be recorded in the patient's medical notes and on the relevant eCRFs. Reasons that a patient may not have surgery include becoming unfit for surgery, deterioration in health, or patient or clinical decision.

In such cases patients will remain within the trial for the purposes of follow-up, QoL assessments and data analysis unless they explicitly withdraw consent. Patients should be followed up as per section 9.7 (Assessments during follow-up).

A surgery form should be submitted even if a patient does not undergo surgery.

15.2 Group 2 patients who have macroscopic residual disease after surgery (R2 resection)

The R stage (residual disease) is required to be reported for Group 2 patients randomised to undergo a hemithyroidectomy or total thyroidectomy on the trial. If a patient has a R2 resection with macroscopic residual disease remaining after the surgery the patient would become ineligible and need to be withdrawn from the trial.

Sites must inform UCL CTC as soon as possible. No further data should be collected on these patients and they should be treated and followed up as per standard of care

15.3 Withdrawal of Consent

If a patient withdraws consent for any aspect of the trial, UCL CTC should be notified and the Change of Status eCRF should be entered on the trial database.

15.3.1 Withdrawal of consent for follow-up

If a patient withdraws consent for trial follow-up, but is willing to continue with future data collection from hospital notes:

- They will remain on trial for follow-up
- The patient will no longer have trial-specific visits and assessments. Follow-up forms should be completed based on the routine visit nearest the due date for the follow-up form
- The following eCRFs/data must be entered at time of withdrawal:
    - Change of Status
    - All CRFs up to and including the date of withdrawal of consent

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- Thereafter, the site should report follow-up forms, including notifications of relapse, death and second malignancy.

15.3.2 Withdrawal of consent for data collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected. The following eCRFs must be entered at the time of withdrawal of consent:

- Change of Status
- All eCRFs up to and including the date of withdrawal of consent

Thereafter, no further data should be submitted.

15.4 Losses to Follow-up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for the patient to be followed up via the patient's GP. Details of participating trial sites can be obtained from the UCL CTC trial team, who must be informed of the transfer of care and follow-up arrangements. If it is not possible to transfer to another participating site, the registering site remains responsible for submission of eCRFs.

If a patient is lost to follow-up, every effort should be made to contact the patient's GP to obtain information on the patient's status.

UK patients who are lost to follow-up will be tracked by UCL CTC via cancer or other national health data registries or databases e.g. NHS Digital.

At the time of loss to follow-up, the following eCRFs should be entered:

- Change of Status
- All eCRFs due up to and including the date of loss to follow-up

If contact is re-established with the patient, further follow-up forms should be sent, including notifications of relapse and second malignancy. A death form should also be submitted if the site becomes aware that the patient has died.

Prior to primary analysis and presentation/publication of the primary endpoint data, UCL CTC may ask sites to attempt to re-establish contact with patients who were lost to follow-up and/or check hospital records for evidence of when the patient was last known to be alive and evidence of death, disease progression or second malignancies.

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16 TRIAL CLOSURE

16.1 End of Trial

For regulatory purposes the end of the trial will be 20 years after the surgery date of the first patient randomised on to the trial. At this point the 'declaration of end of trial' form will be submitted to Ethics Committee, as required, and sites notified.

The initial 6½ years of follow-up data will be obtained from sites then an additional 13 ½ years long term follow-up data on recurrences and mortality will be collected electronically from national health data registries and databases (e.g. NHS Digital).

UCL CTC will advise sites on the procedure for closing the trial at the site once the initial 6½ years of follow-up are complete. Up until formal closure sites must co-operate with any data queries regarding existing data to allow for analysis and publication of results.

Once the end of trial has been declared, no more prospective patient data will be collected.

16.2 Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained securely for a minimum of 5 years after the end of the trial, and in accordance with national legislation.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

16.3 Early Discontinuation of Trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see section 14.3.2 Trial Steering Committee (TSC) and 14.3.3 Independent Data Monitoring Committee (IDMC)). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

16.4 Withdrawal from Trial Participation by a Site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for any patients recruited into the trial at that site and other responsibilities continue as per the site agreement.

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17 STATISTICS

17.1 Sample Size Calculation

The estimated recurrence-free rates for TT in the table below are consistent with the long-term follow-up results from the HiLo trial which included intermediate risk patients (7).

	Recurrence-free rate				
	Trial group		Non-inferiority margin	No. of patients (no. events)	
	TT	HT		80% power	90% power
5 years	95%	90%	5 percentage points	628 (28)	842 (39)
	95%	89%	6	**432 (20)**	578 (26)
3 years	97%	92%	5	234 (10)	314 (14)
	97%	91%	6	162 (7)	216 (10)

(using PASS sample size software: non-inferiority tests for the difference of two hazard rates, using time-to-event data).

The HoT trial will require 432 patients using a non-inferiority margin of 6 percentage points and allowing for a potential 5% loss, so 456 patients in total will be recruited. It assumes a recruitment time of an estimated 79 months with a follow-up of 30 months after surgery, for the first main analysis (so that the minimum follow-up is ~2.5 years for the last patients recruited but ~6.5 years for the first patients recruited); and 2.5% one-sided statistical significance, power 90% and 1:1 randomisation for both patient groups. For a 3-year recurrence-free rate, a trial of 432 patients has >90% power. Many recurrences occur by 3 years, and from the long-term follow-up of the HiLo trial additional recurrences were seen up to 5 years.

The non-inferiority margin was determined by a panel of patients who were given the harms and benefits associated with TT and HT, alongside various options for a margin. The value of 6 percentage points was chosen as being acceptable; and this was also agreed by the trial investigators.
All patients are followed at least annually for life, as per UK guidelines, and because we will also follow-up patients through NCRAS, we expect few loses to follow-up.

17.2 Statistical Analyses

Although the trial is powered for a comparison of the 5-year recurrence rate, the primary endpoint is the recurrence rate at 3 years. Any patient who has a thyroid cancer recurrence, metastatic disease or dies from thyroid cancer (whichever occurs first) will be counted as an event, and all other patients are censored at the date they were last known to be alive. All times are measured from the date of randomisation. This endpoint will be analysed using Kaplan-Meier curves and Cox regression. The difference in recurrence rate (hazard rate) will be obtained and its confidence interval examined to determine whether or not it includes the

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non-inferiority margin (and with a non-inferiority p-value from a test to compare the difference in two event rates, with consideration of the allowable margin). If the confidence interval excludes the margin of 6 percentage points and the one-sided p-value is <0.025, we can conclude that non-inferiority has been achieved.

The primary analyses will be based on a per-protocol dataset, in which only patients who received the randomly allocated surgical method will be included. A second analysis will be based on all randomised patients (intention-to-treat analysis), regardless of whether TT patients actually received HT, or vice versa.

An additional analysis of the 3-year recurrence rate will be based on the hazard ratio from a Cox regression, used to exclude a non-inferiority margin of hazard ratio 3.10 (which corresponds to 3-year event rates of 97% TT vs 91% HT). Also, a competing risk analysis could be performed, to allow for patients who die from causes other than thyroid cancer. These will be done by per-protocol and intention-to-treat analyses.

Secondary endpoints

i. 5 year recurrence rate will be analysed in the same way as 3-year recurrence. An additional analysis of the 5-year recurrence rate will be based on the hazard ratio from a Cox regression, used to exclude a non-inferiority margin of hazard ratio 2.27 (which corresponds to 3-year event rates of 95% TT vs 89% HT).
ii. Anatomical site of recurrences will be compared using a frequency table, and Fishers exact test.
iii. Risk of loco-regional recurrence: based on time to recurrence in the neck only (thyroid cancer metastatic disease and death from thyroid cancer are censored at the date they occur, and all other patients censored at the date last seen alive). This will be analysed using Cox regression.
iv. Number and type of additional investigations and procedures after surgery will be compared using a frequency table, and Fishers exact test.
v. Surgical complications and severity, including voice function: adverse events will be categorised using the CTCAE v5.0 criteria, and the highest grade for each event type for each patient will be obtained. These will be compared using a frequency table, and Fishers exact test where appropriate.
vi. Requirement for hormone replacement therapy: the percentage of patients who require this therapy will be compared between the trial arms using a chi-squared test of two proportions.
vii. Quality of life will be analysed using repeated measures regression analyses (but there is also interest in the 6, 18 and 30 month time points separately). QoL will be transformed into domains (e.g. physical, role, emotional etc for the QLQ-C30), and scored as specified by the organisations that created the QoL instruments. QoL at 2-4 weeks post-surgery is for descriptive purposes only, because not all patients would be seen at this time.

17.3 Economic Evaluation

We will evaluate the cost-effectiveness of HT from a health and social services perspective

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over a 30 month and a lifetime horizon.

Quality of life will be assessed using the EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-THY34 at baseline, post-surgery, 6 months and then annually. Health state values will be calculated from the EQ-5D-5L profiles by applying the new EQ-5D-5L tariff (if published, valuation study is currently in the field) or the cross-walk (41). Cancer-specific health state values will be estimated by mapping the QLQ-C30 and QLQ-THY34 to generate EQ-5D values (note EORTC study in the field (42)), and also by generating QLU-C10D scores from the QLQ-C30 (43). Quality Adjusted Life Years (QALYs) will be estimated for each trial participant by calculating the area under the curve (AUC) joining the health state values at each point in time.

Secondary health care resource use and costs will be derived from data collected from sites on the eCRFs and from data in Hospital Episode Statistics (HES) linked to records on patients held by NCRAS. Primary health and social care resource use will be collected using a patient questionnaire at baseline and each follow-up point and valued using appropriate national unit costs (44). Records of theatre time along with length of stay data from hospital patient records will be used to estimate the cost of HT and TT in combination with unit costs derived from trust level financial data where possible. Costs over time will be aggregated for each individual participant.

Costs and effects that occur in the future (> 1 year) will be discounted in line with current economic evaluation methodology (3.5%) (45). The sensitivity of the results to the discount rate will be tested by varying the rate between 0% and 6% separately for costs and effects. We will report mean costs and QALYs over 30 months for patients receiving HT and TT. Incremental costs and QALYs (difference between interventions) will be estimated after adjusting for selected baseline covariates including baseline EQ-5D-5L (46). Missing data will be imputed using multiple imputation provided assumptions that the data are missing at random are plausible (47). Cost-effectiveness will be reported as the incremental cost-effectiveness ratio (ICER), that is incremental costs divided by incremental QALYs, cost per QALY gained. Uncertainty will be captured by bootstrapping to preserve any correlation between cost and outcome data, and reported as the cost-effectiveness acceptability curve (CEAC) (48). Subgroup analyses will be undertaken for groups 1 and 2. Sensitivity analysis will consider any variability in cost effectiveness when cancer-specific health state values are used to estimate QALYs and cost per QALY.

Lifetime cost-effectiveness will be assessed through the construction of a Markov model to extrapolate costs and quality adjusted life expectancy. The model will capture the recurrence and treatment outcomes of thyroid cancer over the lifetime of patients. Data on costs and quality of life after thyroid cancer recurrence and re-treatment will be informed by the trial data and the literature. Parametric survival analysis of the trial data will be integrated with evidence from the literature to inform estimates of recurrence rates after HT or TT over the lifetime of patients (49). The model will be fully probabilistic and cost-effectiveness will be reported as the mean ICER over 10,000 simulations and the CEAC. Results will be reported by subgroup for groups 1 and 2. Extensive structural sensitivity analysis exploring the impact of alternative assumptions regarding the extrapolation of recurrence rates will be undertaken.

Additional analyses will explore the quality of life of thyroidectomy patients, not just comparisons between HT and TT patients but explorations of how quality of life changes over

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time with recurrence and other clinical events. The inclusion of three quality of life measures will allow for an analysis of the sensitivity to these measures when used in a surgical setting. Panel data econometric approaches will be employed to understand what clinical events and socio-demographics predict quality of life, changes in quality of life and whether and how these differ by instrument.

17.4 Evaluation of the clinical utility of OpenClinica Participate (ePRO software)

This sub-study will have a non-inferiority design based on an expected (optimistic) 85% of patients who complete the PRO by paper, and using electronic QoL (OpenClinica Participate) we allow this to go down to 77.5% (maximum allowable margin of 7.5 percentage points). With 10% one-sided statistical significance, 350 patients has 75% power and 300 patients had 70% power. The outcomes of interest include:

- percentage of patients who complete the questionnaire, at each of baseline, 2-4 weeks post-surgery, and the 6 month and annual visits.
- percentage of questions completed (per patient) for each questionnaire
- timeliness of questionnaire completion via timestamp of form completion relative to the due date
- time taken to complete the questionnaire

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18 ETHICAL CONSIDERATIONS

This trial will adhere to the principles and conditions of Good Clinical Practice.

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with the protocol and with all relevant guidance, laws and statutes, as amended from time to time, applicable to the performance of clinical trials and research including, but not limited to:

- UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority
- Human Rights Act 1998
- Data Protection Act 2018
- UK GDPR (as defined in section 3(10) (as supplemented by section 205(4)) of the Data Protection Act 2018); all applicable law about the processing of personal data and privacy; and (to the extent that it applies) the General Data Protection Regulation (EU)2016/679 (EU GDPR)
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Mental Capacity Act 2005

18.1 Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the London – Bromley Research Ethics Committee (REC) and Health Research Authority (HRA) approval for conduct in the UK.

UCL CTC will submit Annual Progress Reports to the REC, commencing one year from the date of ethical approval for the trial.

18.2 Site Approvals

Evidence of assessment of capability and capacity by the Trust/Health Board R&D for a trial site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

18.3 Protocol Amendments

UCL CTC will be responsible for gaining ethical approval for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

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Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments promptly.

18.4 Patient Confidentiality & Data Protection

Patient identifiable data, including initials, date of birth, ethnicity, NHS/CHI number and full post code will be collected by UCL CTC via OpenClinica (OC) a remote electronic data capture system used in Clinical Research. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 2018 and GDPR, with the Data Protection Officer at UCL.

Twilio and Sinch (also known as Mailgun) are sub-processors of OC. Patient identifiable data will be provided to Twilio (patient name and mobile telephone number) and Sinch (patient name and email address). They will use these details in order to send text messages (Twilio) and/or emails (Sinch) to invite patients to complete online quality of life questionnaires. Twilio will process data for sending invitations in the US, where data protection laws have different levels of protection to those in the UK and EU/EEA. Sinch will process data in the EU. Twilio and Sinch are required not to use patient identifiable data for any purposes other than those detailed above. They will not share personal information with any other organisation, they will hold it securely and retain it only for the period required to process the data. UCL CTC will not have access to the patient identifiable data provided for this purpose.

Patient identifiable data, including initials and trial number will be provided to pathology laboratories performing central histological review. These laboratories will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified.

Patient trial number, date of birth and NHS/CHI number will be provided to national health data registries and databases (e.g. NHS Digital/ISD Scotland) so that they can provide long-term follow-up data. All data shared with these organisations will be handled under strict rules covering data protection and confidentiality and they will not disclose or reproduce any information by which patients could be identified. Patient ethnicity and postcode will be collected to help us assess whether participants from different backgrounds and socioeconomic status are taking part in our study.

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19 SPONSORSHIP AND INDEMNITY

19.1 Sponsor Details

Sponsor Name:	University College London
Address:	Joint Research Office 4th Floor, West 250 Euston Road, London NW1 2PG
Contact:	Managing Director, UCL/UCLH Research
Tel:	020 3447 9995/2178 (unit admin)
Fax:	020 3447 9937

19.2 Indemnity

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.
Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

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20 FUNDING

This project is funded by the National Institute for Health Research (NIHR) (HTA Project NIHR 128699). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

After the trial follow-up has ended an additional 13 ½ years of long-term follow-up data will be collected on recurrences and mortality through national registries and databases (e.g. NCRAS). OpenClinica Participate are providing the web-based app and the sub-study will be managed by UCL CTC.

The nested sub-study testing the clinical utility of OpenClinica Participate web-based app (software) will not be funded or commissioned by NIHR. Management of the sub-study will be funded by UCL CTC.

Research costs will be reimbursed to sites as per the finance section of the site agreement.

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21 PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the Trial Management Group. The TMG will form the basis of the writing committee and advise on the nature of the publications. Named authors should include the Chief Investigator, Trial Coordinator(s), Statistician(s) and members of the TMG involved in the trial. Other key contributors to the trial will be acknowledged as appropriate. Data from all sites will be analysed together and published as soon as possible. Participating sites may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. The trial data is owned by the TMG.

The ISRCTN identifier and NIHR grant number allocated to this trial will be quoted in any publications resulting from this trial.

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APPENDIX 1: EXPECTED POST-SURGICAL ADVERSE REACTIONS

The following adverse reactions, to be reported according to CTCAE v5.0, are associated with hemithyroidectomy and total-thyroidectomy and will be considered expected for these surgeries. This list will serve as reference safety information for safety reporting procedures in relation to the trial surgery, has been agreed by the TMG and is derived from the following references:

1. Tolley NS. British Association of Endocrine & Thyroid Surgeons. Patient Information Leaflet T2. Potential consequences of Thyroid Surgery. 2019 Jan.
https://www.baets.org.uk/wp-content/uploads/Patient-Information-Leaflet-T2-Consequences-of-Thyroid-Surgery.pdf

2. Chadwick D, Kinsman R, Walton P. The British Association of Endocrine and Thyroid Surgeons Fifth National Audit Report: Dendrite Clinical Systems Ltd; 2017. 98-99.
https://www.baets.org.uk/wp-content/uploads/BAETS-Audit-National-Report-2017.pdf

3. De Groot LJ, Bartalena L, Feingold KR. Thyroid Storm. [Updated 2018 Dec 17]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278927/

Post-Surgical Adverse Reactions - CTCAE v5.0 Terms	
System Organ Class - Respiratory, thoracic and mediastinal disorders	*System Organ Class - Nervous system disorders*
• Voice alteration • Hoarseness • Aphonia • Sore throat • Dyspnea • Tracheal fistula • Upper Respiratory Infection	• Recurrent laryngeal nerve palsy • Paresthesia • Tremor • Dizziness • Headache • Stroke
System Organ Class - Endocrine disorders	*System Organ Class - Metabolism and nutrition disorders*
• Hypoparathyroidism • Hyperthyroidism	• Hypocalcemia • Dehydration
System Organ Class - Musculoskeletal & connective tissue disorders	*System Organ Class - Cardiac disorders*
• Myalgia • Neck pain • Back pain	• Sinus tachycardia • Ventricular tachycardia • Myocardial infarction

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System Organ Class - Injury, poisoning and procedural complications	System Organ Class - Gastrointestinal disorders
• Intraoperative head and neck injury • Postoperative hemorrhage • Wound complication • Wound dehiscence • Other – anesthesia related complication	• Dysphagia • Nausea • Vomiting • Diarrhea • Esophageal fistula
System Organ Class - Eye disorders	System Organ Class - Infections & infestations
• Blurred vision	• Wound infection
System Organ Class - General disorders & administration site conditions	System Organ Class - Vascular disorders
• Chills • Fatigue • Fever • Pain	• Hematoma • Thromboembolic event • Lymph leakage • Seroma
System Organ Class - Skin & subcutaneous tissue disorders	System Organ Class - Psychiatric disorders
• Hyperhidrosis • Pruritis	• Delirium

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APPENDIX 2: PROTOCOL VERSION HISTORY

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
1	18/03/2021	N/A	N/A	N/A
2	24/05/2021	N/A	Cover page	IRAS number added as requested by the REC
			Page 2	Other trial contacts & TMG sections: Chief Investigator's organisation/address updated
			1.1	Typographical error corrected under endpoints associated with Navio app sub-study
			5	Clarification on process of obtaining informed consent.
			7.1 & 11.1	To limit personal data collection references to 'full name' replaced with 'first name and initial of surname'.
			Throughout	Administrative changes correcting typographical, grammatical and formatting errors.
3	21/09/2021	1	Cover page 2	Sponsor Director removed from Authorisation Signatures
			Appendix 1 & 2	Appendix 2 (Expected Post-Surgical ARs) replaces Appendix 1 (Abbreviations) which has now been moved to start of protocol. Appendix 2 is now Protocol Version History.
			9.1	Typographical error in Schedule of Assessments table corrected
			11.4 & 11.6	Data management guidance updated
			20	NIHR disclaimer amended to correct statement
			Throughout	Administrative changes correcting typographical, grammatical and formatting errors.
4	16/11/2021	2	1.1	Updated in line with changes to section 6.2.1.
			3	Analysis plans on Navio app sub-study phase 1 updated.
			6.2.1	Grammatical changes to make inclusion/exclusion criteria clearer.
			9.1	Schedule of Assessments table updated in line with changes to Section 9.2

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Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
			9.2	Informed consent constraint 'Within 14 days prior to randomisation' removed.
			9.5	Reference to Surgery eCRF recording surgery related mortality removed.
			9.63 & 9.7	Minor clarifications to post-surgical complications assessments.
			11	Reference to trial specific OpenClinica database for EDC added.
			12	Clarification on safety reporting: Sites to report ARs related to pre-trial/on-trial thyroid surgery (i.e. all trial arms) & report SARs related to on-trial thyroid surgery only (i.e. trial arms excluding 'Prior HT+Surveillance' arm).
			15.2	Instruction added: site staff to inform UCL CTC ASAP if a patient becomes ineligible after R2 resection
			Throughout	Further details of personal data collection at Scottish sites added: Reference to CHI number & ISD Scotland.
			Throughout	Administrative changes correcting typographical, grammatical and formatting errors.
5	31/10/2022	4	Cover page	NCRI logo updated
			Cover page & 1.1	ISRCTN number added
			Page 2	TMG Members updated
			Page 2 & 7.1	HoT Trial Coordinator telephone number updated
			4.1.2, 4.2.2, 14.1	Updated in line with HRA guidance which states that research teams conducting non-CTIMPs are expected to be qualified by education, training or experience but should not be required or expected to undertake GCP training.
			5	Addition of option for remote consent if consent cannot be taken in person.
			1.1 & 6.2.1	Clarification added to inclusion criteria for group 1 papillary thyroid cancer patients regarding vascular invasion

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Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
			1.1 & 6.2.1	Terminology updated for non-invasive encapsulated FVPTC (eFVPTC) to NIFTP (non-invasive follicular thyroid neoplasm with papillary-like nuclear features)
			7.1	Instruction for sites to send GP letter added
			7.1 & 11.1	Update to Navio personal data collection where references to 'first name and initial of surname' have been replaced with 'first name and surname'
			8.2.2	Pre-trial HT must be within 6 months of randomisation
			9.1	Schedule of assessments updated to reflect change in section 9.3.
			9.3	Post-randomisation timepoint not applicable for patients whose pre-trial hemithyroidectomy is greater than 4 months ago at randomisation
			9.7.1 & 20	Correction on long-term follow up data being collected for an additional 13 ½ years
			11 & 18.4	Added reference to collection of full postcode and ethnicity to assess participants' background and socioeconomic status
			11.1	Clarification on transfer of Navio data to UCL CTC
			14.3.4	Updated to clarify that the CTC Director is the custodian of the data
			19.1	Updated with new address of UCL JRO
6	28/02/2023	6	Page 2	TMG members updated
			9.1 & 9.2	Window for pre-randomisation clinical examination and WHO performance status increased to 3 months
			9.5 & 9.6.2	Information on readmission within 30 days of surgery moved from post-surgery (prior to discharge) to post-surgery (2-4 weeks)
7	08/07/2024	13	Cover page	NIHR logo updated Cancer Research UK logo updated
			Page 2 & 3	TMG members updated

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Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
			1.1, 2.2, 3, 7, 7.1, 9.1, 9.3, 9.4, 9.6.2, 9.7.1, 11.1 & 17.4	ePRO software for sub-study changed from Navio to OpenClinica Participate
			1.1, 3.2 & 18.4	Updated sub-study endpoints
			3.1 & 17.4	Updated sub-study objectives
			1.1 & 6.2.3	Removed sub-study eligibility criteria
			7.1 & 10.2	Updated job title
			20	Removed reference to Navio
8	18/08/2025	17	Page 1	Senior Project Manager details updated
			Page 2 & Section 7.1	HoT Trial Manager telephone number updated
			Page 2 & 3	TMG Members updated
			1.1 & 6.21	Terminology updated from "oncocytic or *Hürthle cell carcinoma" to "oncocytic (Hürthle cell) carcinoma"*
			Page 11 & Section 17.1	Duration of recruitment updated from "48 months" to "estimated 79 months"
			3.1 & 20	Reference to Navio changed to OpenClinica Participate
			12.2.3	Causality has been updated to Sponsor Clinical Review to reflect that clinical reviewer will not be asked about causality but if there are any safety concerns or queries for site.
			18	Removed typo and updated UK GDPR listing.

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