TRIAL PROTOCOL

RABBIT

Radiofrequency Ablation of Benign Intrathyroidal Tumours

A pragmatic multicentre, randomised trial to examine the clinical and cost-effectiveness of radiofrequency ablation versus hemithyroidectomy in the treatment of benign symptomatic thyroid nodules.

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number: 4.0

Version Date: 16-Apr-2026

PROTOCOL DEVELOPMENT

Protocol amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version. Amendments to the protocol will be made in collaboration with the TMG and the Sponsor will decide if the amendment is substantial or non-substantial. Amendments will be communicated to REC & or HRA as appropriate by completion of the amendment tool and approvals will be emailed to Trust's R&D departments. The amendment history will be tracked within the protocol using the table below.

Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**
01	*21-May-2026*	*4.0*	*Substantial Amendment*	Removal of reference to RFA equipment supplier Clarification and simplification of training requirements for RFA Addition of relevant reference numbers and website links Vocal cord mobility and US at screening – removal of 'within 6 months prior to consent' timepoint Vocal cord mobility assessment, thyroid function test, INR test may be performed after consent has been obtained In the eligibility criteria: ○ Increased nodule size criterion to **65cm^3** and clarification of the 'initial USS' timepoint ○ Removal of aPTT test ○ Re-phrasing 'Absence of retrosternal content' to 'Absence of substantial retrosternal content'

				Transition to entering screening-log data online

Funding and support in kind	
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Funding scheme	**Funder's reference number**
NIHR HTA (Health Technology Assessment)	NIHR135261
This study is funded by the NIHR HTA programme as referenced above. It was designed following a commissioning brief released by the NIHR HTA.	

PROTOCOL SIGN OFF

Chief Investigator (CI) signature page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

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

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

Trial name:	**R**adiofrequency **Ab**lation of **B**enign **I**ntrathyroidal **T**umours (RABBIT)
Protocol version number: Protocol version date:	Version: __ __ __ __ / __ __ / __ __ __ __
CI name:	Mr Neil Sharma
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor statement

By signing the IRAS form for this trial, University of Birmingham, acting as sponsor, confirm approval of this protocol.

Compliance statement

This protocol describes the RABBIT trial only. The protocol should not be used as a guide for the treatment of patients not taking part in the RABBIT trial.

The trial will be conducted in compliance with the approved protocol, the UK Policy Framework for Health and Social Care Research, Data Protection Act 2018 and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) signature page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

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

Trial name: Protocol version number:	Version: __ __
Protocol version date:	__ __ / __ __ / __ __ __ __
PI name:	
Name of Site:	
Signature and date:	_____ __ __ / __ __ / __ __ __ __

ADMINISTRATIVE INFORMATION

Reference Numbers	
Sponsor number	RG_21-192
ISRCTN reference number	10838673
IRAS reference number	335450

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Trial social media	www.twitter.com/TheRabbitTrial

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
BCTU	Birmingham Clinical Trials Unit
CI	Chief Investigator
eCRF	Electronic Case Report Form
DCF	Data Clarification Form
DMC	Data Monitoring Committee
DSA	Data Sharing Agreement
ENT	Ear Nose and Throat
HRA	Health Research Authority
ICER	Incremental Cost-effectiveness Ratio
ICF	Informed Consent Form
INR	International Normalised Ratio
ISF	Investigator Site File
MCIC	Minimum Clinically Important Change
mmHg	Millimetres of mercury
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Public and Patient Involvement
PROM	Patient Reported Outcome Measures
PSS	Personal Social Services
QALY	Quality-Adjusted Life Years
QoL	Quality of Life
REC	Research Ethics Committee
RFA	Radiofrequency Ablation

RGT	University of Birmingham Research Governance Team
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSDL	Site Signature and Delegation Log
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSH	Thyroid Stimulating Hormone
UoB	University of Birmingham
US	Ultrasound scan
VAS	Visual Analogue Scale

TRIAL SUMMARY

Title

A pragmatic multicentre, randomised trial to examine the clinical and cost-effectiveness of radiofrequency ablation (RFA) versus hemithyroidectomy in the treatment of benign symptomatic thyroid nodules

Objectives

To examine the efficacy of radiofrequency ablation versus conventional open hemithyroidectomy for symptom reduction, complications, cost effectiveness and overall acceptability.

Trial design

A pragmatic, multicentre, open label, randomised non-inferiority trial, with 1:1 randomisation, including an internal pilot phase and a health economic evaluation.

Participant population and sample size

448 patients aged 18 years or older with single or multiple thyroid nodule(s) that are causing compressive or cosmetic symptoms affecting their quality of life.

Setting

Secondary/Tertiary Care thyroid surgery/endocrinology departments in approximately 20 UK centres

Eligibility criteria

Inclusion

- Age ≥18 years
- Thyroid nodule assessed as benign on an ultrasound scan (US) *and* fine needle aspiration cytology (FNAC) (U2/TIRADS2 *and* 1 X Thy2 OR U3/TIRADS3 *and* 2 x Thy2)
- Nodule criteria:
    - Total volume of nodule ≤ 65cm^3 at time of initial US
    - Nodule consistency: Either 1) Solid, 2) Mixed solid and cystic (≤60% cystic), or 3) Microcystic (0-100%)
    - Absence of substantial retrosternal content
- Clinical/radiological evidence of compression or cosmetic concerns ascribed to unilateral thyroid nodule/s and NOT to bilateral nodules or diffuse goitre
- Thyroid Stimulating Hormone (TSH) >0.1mIU/L and <upper limit of local reference range
- Free T4 within local reference range if TSH >0.1 mIU/L and < lower limit of local reference range
- International Normalised Ratio (INR) ≤1.5
- Willing and able to provide written consent
- Willing to undergo randomisation

Exclusion

- Contraindication to thyroid surgery or RFA
- Any previous surgery to the central neck compartment
- Previous treatment for thyroid disorders

- Previous thyroid RFA
- Previous radioactive iodine treatment
- Previous radiotherapy which included the neck
- Current treatment with antithyroid drugs or thyroid hormone replacement
- Known pregnancy
- Formal anticoagulation that cannot be paused for the intervention, or documented bleeding diathesis
- Clopidogrel that is not able to be stopped for a minimum of 5 days prior to the intervention
- Aspirin that is more than the maximum dose of 75 mg once daily
- Prosthetic heart valve, pacemaker, or any other implanted cardiac device
- Other malignant nodules or nodules with indeterminate cytology in either lobe
- Pre-existing vocal cord palsy

Interventions

Radiofrequency ablation versus conventional open hemithyroidectomy

Outcome measures

Primary outcomes

- Goitre symptom score (goitre domain of the ThyPRO)

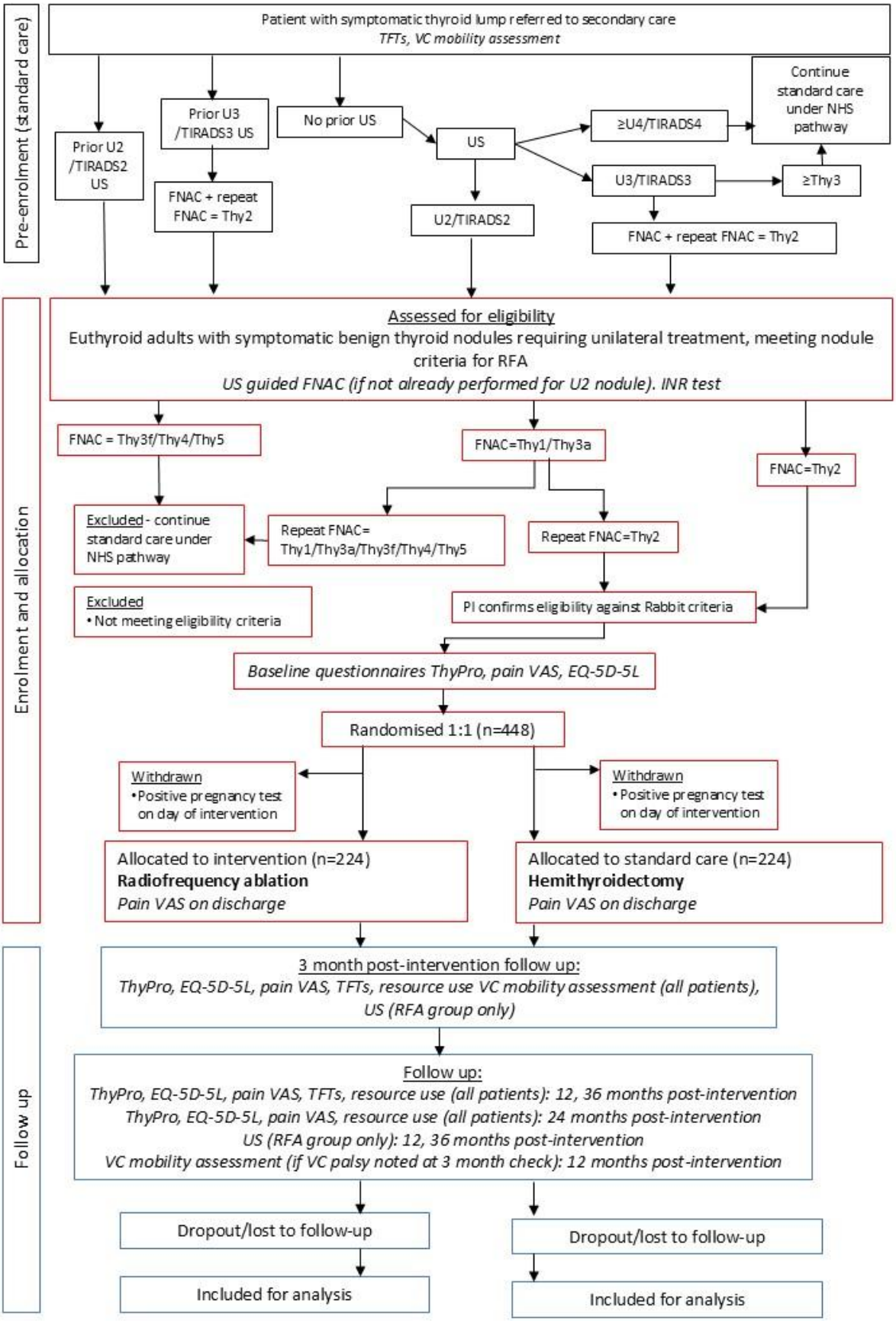
Secondary outcomes

- Composite ThyPRO score
- All other domain ThyPRO scores
- Complication rate
- Hypothyroidism
- Recurrent laryngeal nerve palsy
- Percentage volume reduction in treated nodule
- Need for additional related procedures
- Nodule recurrence
- Pain intensity (Pain visual analogue scale, VAS)
- Related re-admission
- Health related quality of life (EQ-5D-5L)
- Health resource usage (HRUQ)
- Acceptability of RFA to patients

Health economic outcome

- Cost effectiveness

Trial Schema



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1. BACKGROUND AND RATIONALE

1.1 Background

Prevalence of thyroid nodules

Thyroid nodules are very common and are identified by clinical examination in 5-7% and by high resolution US in 50-60% of people. They are 3-4 times more prevalent in women than in men and more common in iodine deficient regions and older populations. Most thyroid nodules are asymptomatic, although some patients may have symptoms of compression including globus sensation (feeling of a lump/foreign body in the throat), dysphagia (difficulty swallowing), dyspnoea (difficulty breathing especially when lying flat), and sometimes pain over the nodule. In addition, some patients report concerns about the cosmetic effects of large neck swellings **(1, 2)**.

Approximately 5% of thyroid nodules are hyperfunctioning causing hyperthyroidism (thyroid gland overactivity) and around 5-10% of thyroid nodules are malignant (1, 2). National and international guidelines recommend the determination of thyroid function and assessment of malignancy risk in thyroid nodules that are detected clinically or incidentally on cross-sectional imaging for non-thyroid related diseases. Most thyroid nodules that are associated with normal thyroid function and considered benign following evaluation do not require further assessment or treatment, unless there is symptomatic/biochemical change. Nodules that cause compressive symptoms may require treatment to relieve the compression **(3-5)**.

Diagnostic evaluation of thyroid nodules

Thyroid nodules should be assessed through measurement of thyroid function (serum thyrotropin [TSH] and circulating thyroid hormones, free thyroxine [fT4] +/- free triiodothyronine [fT3]) and ultrasonographic evaluation to determine the risk of malignancy. Based on the US assessment, a fine needle aspirate may be taken for cytological assessment (FNAC) to further refine the malignancy risk **(1-3)**.

There are a number of US classification systems in use. In the UK, the U-classification **(4)** and ACR-TIRADS **(6**) are most commonly used. These systems evaluate ultrasonographic nodule characteristics that are associated with malignancy including solid composition, irregular nodule margins, hypo-echogenicity, presence of microcalcifications, internal vascularity and wider than tall shape in the transverse plane. This provides an overall score which is linked to the risk of malignancy. The TIRADS system also takes nodule size into account when deciding which nodules require FNAC (see table 1).

TIRADS Score	**FNAC considered**	**U classification**	**FNAC considered**
TR1 benign	No	U1 normal thyroid	No
TR2 not suspicious	No	U2 benign nodule	No
TR3 mildly suspicious	if ≥ 2.5 cm	U3 indeterminate	Yes
TR4 moderately suspicious	if ≥ 1.5 cm	U4 suspicious	Yes

TR5 highly suspicious	if ≥ 1.0 cm	U5 malignant	Yes

Table 1: The decision-making algorithms used to decide which nodules require FNAC

U1 classification means there is a normal thyroid with no nodule present. Nodules that are TR1 or TR2 or U2 are deemed benign. U1 and TR1 nodules are not considered for the RABBIT trial. Nodules that are TR3/TR4/TR5 or U3/U4/U5 may be malignant. The cytological THY classification **(7)** further refines the malignancy risk and those that are stratified as Thy3/Thy4/Thy5 require diagnostic surgery to determine presence of malignancy (see table 2). Nodules that are TR3/U3 and have benign Thy2 cytology require a second FNAC to confirm benign features **(4).**

Thy Score	**Interpretation**	**Suggested course of action**
Thy 1	Insufficient sample	Repeat FNAC
Thy 2	Benign	None
Thy 3a	Atypical cells present	Repeat FNAC
Thy 3f	Follicular thyroid lesion	Diagnostic thyroidectomy
Thy 4	Suspicious for malignancy	Diagnostic thyroidectomy
Thy 5	Malignant	Diagnostic thyroidectomy

Table 2: The cytological THY classification and malignancy risk and treatment required

Treatment of benign compressive thyroid nodules

Thyroid nodules that cause compressive or significant cosmetic symptoms have historically been treated with surgery, usually in the form of conventional open hemithyroidectomy (hereafter referred to as hemithyroidectomy for the purposes of the RABBIT trial protocol). In recent years, several thermal ablation techniques have been developed; these are minimally invasive procedures that avoid removal of the thyroid gland and target symptomatic nodules directly **(8, 9**). Internationally, RFA is the most widely used of these techniques and has been approved by the National Institute for Health and Care Excellence (NICE) **(10)**.

The short-term efficacy (at 6-12 months) and safety of RFA for volume reduction in benign euthyroid nodules is estimated at 50-80% as demonstrated in prospective observational studies **(11-15**), randomised controlled trials of RFA versus observation **(16, 17)** and systematic reviews **(18, 19).** Longer term data are starting to emerge, indicating progressive shrinkage with nodule volume reduction reported as 67-93% **(20-22)** at 5 years post RFA and nodule re-growth rates reported between 5.3-20% **(21, 22)**. The best volume reduction rates are obtained in smaller nodules (78-82% in ≤10-12 mL vs 62-65% in 20-30 mL lesions), with larger nodules more likely to require more than one treatment **(8, 9, 16, 17).**

Whilst RFA is considered a safe technique there is a small risk of complications which are mostly minor and include pain (2.6-17.5%), transient voice change (<1%), and less commonly skin burns, haematoma and transient thyroiditis (<0.5%). Major complications such as permanent recurrent laryngeal nerve injury, nodule rupture, haematoma requiring surgical drainage, Horner's syndrome

or injury to the adjacent oesophagus or trachea are rare **(9, 23-27)**. When comparing thermal ablation with conventional thyroidectomy, a meta-analysis suggested that thermal ablation was safer and associated with lower incidence rates of hoarseness, hypothyroidism and post-operative pain ($p<0.05$). Patients treated with RFA also had improved post-operative cosmetic outcomes, better patient satisfaction and quality of life scores, as well as shorter hospitalisation time compared with thyroid surgery ($p<0.05$) **(27)**. However, symptom improvement was not different between thermal ablation and surgery **(27, 28)**, indicating that RFA may be as effective at reducing compressive symptoms as surgery **(9).**

When comparing complication rates, RFA has been shown to be superior to surgery with no cases of post-intervention hypothyroidism in RFA treated patients versus 37.5% in those undergoing hemithyroidectomy **(29)**. Hypothyroidism occurs in 20-30% of patients undergoing hemithyroidectomy, which results in the need for life-long replacement treatment with thyroid hormones and significantly reduced quality of life (QoL) **(30, 31)**. In addition, the risk of recurrent laryngeal nerve damage (3% vs 0.5%) and hypoparathyroidism (3% vs 0%) are significantly higher in those undergoing surgery compared with RFA **(18)**.

Tools to measure quality of life in patients with thyroid diseases

ThyPRO is a well validated and internationally accepted thyroid-specific health-related patient reported outcome tool which is recommended for the assessment of patients with benign thyroid diseases in view of its internal consistency, content validity, and structural validity **(32, 33)**. Several studies have confirmed the utility of ThyPRO in assessing alterations in symptoms and quality of life following surgery for benign thyroid enlargement **(34-37)**. The ThyPRO tool measures a range of aspects of QoL relevant to patients with benign thyroid diseases. It consists of 84 items summarised in 13 scales, as well as a single composite item measuring overall impact of thyroid disease on QoL. The 13 ThyPRO scales are: goitre symptoms, hyperthyroid symptoms, hypothyroid symptoms, eye symptoms, tiredness, cognition, anxiety, depressivity, emotional susceptibility, impaired social life, impaired daily life, impaired sex life, cosmetic complaints, and overall quality of life (this last being a standalone question not contributing to the composite score). Each item is rated on a 0-4 Likert scale from no symptoms/problems = 0 to severe symptoms/problems = 4. The average score of items in a scale is divided by 4 and multiplied by 100 to yield 13 scales ranging from 0-100 with higher scores indicating worse health status **(30)**.

A shorter version of the ThyPRO tool has been developed which consists of 39 items **(38)**. This shortened version has significantly fewer questions related to goitre symptoms, which is the most important scale in the patient group that we are evaluating. Importantly, the full ThyPRO questionnaire has been translated and validated in several other languages including Hindi, Arabic, Chinese **(39)**, Polish, Spanish **(40)** and German **(41)** allowing its use in multi-ethnic and multicultural societies such as the UK. The interpretability of ThyPRO has been improved by the establishment of Minimal Important Change (MIC) values thereby providing estimates of which changes are clinically relevant **(42).**

To assess post-operative pain, the use of Visual Analogue Scales (VAS) is well-validated for patients before and after thyroid-related interventions **(43-45).**

1.2. Trial rationale

This trial has been developed in response to a HTA commissioned call to directly compare hemithyroidectomy with percutaneous thermal ablation of benign thyroid nodules. This forms the rationale for the trial.

Why is this research needed now?

Benign thyroid nodules are common, may be symptomatic and constitute a significant burden on the NHS.

Thyroid nodules may be identified by patients through a combination of cosmetic and compressive symptoms or picked up on imaging when investigating dyspnoea or dysphagia. The location of the thyroid in the lower anterior neck and its direct proximity to the trachea and oesophagus can result in compressive symptoms when part or all of the gland is enlarged. These symptoms may be severe, and lead to significant airway compression and emergency surgery, although most patients will report progressive dysphagia and dyspnoea when lying flat on their back. Patient reported problems are the best indicator of whether treatment would reduce symptoms; clinical examination or ultrasonography alone are poor predictors of symptoms.

Data from the British Association of Endocrine and Thyroid Surgeons show that approximately 1,110 hemithyroidectomies are performed annually for benign compressive symptoms, although this figure is likely to be higher as more than 50% of thyroid surgeries in the UK are not recorded on this database **(46)**. The estimated cost to the National Health Service (NHS) is £7.4 million per year **(47)**. Hemithyroidectomy carries significant risks relating to general anaesthesia, wound infection, haematoma formation requiring surgical evacuation and recurrent laryngeal nerve damage resulting in swallowing and voice dysfunction **(48)**. This risk lies between 9-10% for temporary injury (up to 6 months), and around 1% for permanent injury. Injury to the nearby superior laryngeal nerve also results in voice change, and is especially noticeable in patients who use their voice regularly for work **(48)**. It is estimated that around 20-30% of patients undergoing hemithyroidectomy develop permanent hypothyroidism requiring life-long replacement therapy with levothyroxine **(49)**. All of these complications result not only in harm to patients, but also further resource use for the health service.

Lower surgical prioritisation for benign thyroid nodules.

The benign nature of thyroid nodules is confirmed using US and FNAC; a US grade of “U2'' and FNAC grade of “Thy2” is sufficient **(4)**. Patients with benign symptomatic nodules are, appropriately, prioritised below those with suspected cancer or significant airway obstruction. Many have lengthy delays before surgery and a significantly reduced quality of life **(50).** Hemithyroidectomy results in risks and burden to patients, in addition to significant resource cost to the health service: post-thyroidectomy patients stay at least one night in hospital with some requiring two or more night stays.

Importance of the proposed study.

In the post COVID-19 era, with significant backlogs and delays to all forms of surgery in the UK **(51)**, a new treatment paradigm is needed for patients with benign, symptomatic thyroid enlargement. The

opportunity and benefits to patients and the health service presented by the approval of RFA for thyroid nodules by NICE is significant **(10).** Although many radiologists in the UK have received training to undertake the procedure, the lack of clear evidence for equipoise with surgery in terms of symptom reduction, as well as absence of data regarding cost effectiveness, has led to a slow uptake nationally.

The proposed research is crucial as it will provide an evidence base for the use of RFA compared to open surgery for the management of benign thyroid nodules. If the primary outcome of a randomised trial demonstrates that RFA is not inferior to surgery for symptom reduction and is more cost effective, as well as, secondarily, at least as good as or better for complications, then it would promote the wide use of RFA across the UK for benign thyroid disease, serve patients better and be cost-efficient.

1.2.1. Justification for participant population

The participant population will consist of patients aged 18 years or older with single or multiple thyroid nodule/s that are causing compressive or cosmetic symptoms affecting their QoL.

The thyroid nodules must be benign due to the fact that thyroid RFA is only approved for benign nodules in the UK. The evidence regarding its use in thyroid malignancy is scant and the commissioning brief specifically calls for a study involving benign nodules only.

The commissioning brief also specifies that patients should be symptomatic from their thyroid nodule/s.

1.2.2. Justification for design

Randomised trials provide a high level of evidence for clinical research. To date, there have been no studies directly comparing RFA to open surgery in a randomised setting, therefore this trial seeks to provide high quality evidence as to the effectiveness of RFA compared to hemithyroidectomy in this setting. A non-inferiority design was chosen because surgery results in complete removal of the thyroid nodule and is therefore almost guaranteed to reduce goitre symptoms (the primary outcome). RFA results in reduction of nodule volume rather than complete removal and, while it is still expected to improve compressive symptoms, RFA may not reduce goitre symptoms to the same extent as surgery. We anticipate that RFA may be non-inferior to surgery at reducing compressive symptoms (2).

The trial aims to be as pragmatic as possible, with wide inclusion criteria to demonstrate generalisability to a wide group of patients and centres, while keeping within clear boundaries to ensure patient safety.

Given the nature of the intervention, it is not possible to blind the clinical teams or the participant to the randomised allocation, so the participant reported outcomes will be completed with knowledge of treatment allocation. However, as all participants receive an active treatment (either RFA or surgery) this may mitigate the extent of bias in patient reported outcomes.

1.2.3. Justification for choice of intervention

While a number of ablative techniques exist (radiofrequency, microwave, laser, high frequency US, ethanol), RFA is the most widely used technique and is the one that has demonstrated the most consistent results in terms of nodule volume reduction. In addition, RFA has been recently approved by NICE in the treatment of benign thyroid nodular disease, yet the uptake in many centres in the UK is slow, limited by the lack of evidence that it is a safe and cost-effective treatment method.

1.2.4. Justification of choice of primary outcomes

The choice of primary outcomes has been guided by:

- The HTA commissioning brief
- Existing literature
- Consultation with expert clinicians across all relevant disciplines
- Views of patients, patient support groups, and lay focus groups

The goitre domain of the ThyPRO questionnaire was chosen as the primary outcome based on feedback from our focus groups. They indicated that the questions contained within the "goitre" domain of ThyPRO were most in keeping with the concerns that patients had and would fulfil the commissioning brief for the primary outcome. The 12 month time point at which goitre symptom score should be assessed was chosen as literature suggests that nodule reduction can continue to occur throughout the first year following RFA. Further reduction can take place subsequently albeit less frequently. Twelve months was also thought to represent a time point at which patients should have fully recovered from hemithyroidectomy.

The trial will also assess the cost-effectiveness of RFA compared to open surgery, which will facilitate the approval of the technique in a more widespread manner across the UK, and further afield.

2. AIMS AND OBJECTIVES

To examine whether RFA is non-inferior to hemithyroidectomy for symptom reduction and complications and is cost effective, and to assess the acceptability of RFA in the treatment of benign nodular goitre.

2.1. Internal pilot objectives

The aims of the 6 month internal pilot phase are to test the ability to recruit, consent, and randomise participants.

The main objectives of the pilot phase are to achieve:

- Accrual of 84 participants in 6 months
- Opening of 12 sites at a rate of 2 sites per month

The internal pilot phase will also enable us to identify any other logistical issues and take appropriate measures to address them.

2.2 Main trial objectives

To compare the clinical and cost effectiveness of RFA compared to hemithyroidectomy in the reduction of symptoms attributable to benign thyroid nodules, and to compare the complication rates for the two treatment modalities.

2.2.1 Clinical aims and objectives

Primary objectives:

- To evaluate the efficacy of RFA, compared to hemithyroidectomy:
    - In the treatment of symptoms attributable to benign nodular goitre, measured by the goitre domain of the ThyPRO tool 12 months after the intervention

Secondary objectives

- To compare RFA to hemithyroidectomy for:
    - Thyroid related quality of life
    - Incidence of complications
    - Pain
    - Need for additional procedures
    - Related readmission
- To assess nodule percentage volume reduction following RFA
- To assess nodule recurrence rate following RFA
- To assess the acceptability of RFA to patients

2.2.2 Economic evaluation aims and objectives

Primary objective:

- To evaluate the cost-effectiveness 12 months after the intervention of RFA, compared to hemithyroidectomy.

3. TRIAL DESIGN AND SETTING

3.1. Trial design

A pragmatic, multicentre, open label, randomised non-inferiority trial, with 1:1 randomisation, including an internal pilot phase and a health economic evaluation.

3.2. Trial setting

The trial will take place in approximately 20 secondary and tertiary care hospitals in the UK.

3.3. Assessment of risk

All clinical trials can be considered to involve an element of risk and in accordance with the Birmingham Clinical Trials Unit (BCTU) standard operating procedures (SOP), this trial has been risk assessed to clarify any risks relating uniquely to this trial beyond that associated with usual care. A Risk Assessment has been conducted and concluded that this trial corresponds to the following categorisation:

No higher than the risk of standard medical care.

4. ELIGIBILITY

4.1. Inclusion criteria

- Age ≥18 years
- Thyroid nodule assessed as benign on a US *and* FNAC:
    - U2/TIRADS2 (TR2) *and* 1 X Thy2

    OR

    - U3/TIRADS3 (TR3) *and* 2 x Thy2
- Nodule criteria:
    - Total volume of nodule ≤ 65cm^3 at time of initial US
    - Nodule consistency: Either 1) Solid, 2) Mixed solid and cystic (≤60% cystic), or 3) Microcystic (0-100%)
    - Absence of substantial retrosternal content
- Clinical/radiological evidence of compression or cosmetic concerns ascribed to unilateral thyroid nodule/s and NOT to bilateral nodules or diffuse goitre
- TSH >0.1mIU/L and <upper limit of local reference range
- Free T4 within local reference range if TSH >0.1 mIU/L and < lower limit of local reference range
- INR ≤1.5
- Willing and able to provide written consent
- Willing to undergo randomisation

4.2. Exclusion criteria

- Contraindication to thyroid surgery or RFA
- Any previous surgery to the central neck compartment
- Previous treatment for thyroid disorders
- Previous thyroid RFA
- Previous radioactive iodine treatment
- Previous radiotherapy which included the neck
- Current treatment with antithyroid drugs or thyroid hormone replacement
- Known pregnancy
- Formal anticoagulation that cannot be paused for the intervention, or documented bleeding diathesis
- Clopidogrel that is not able to be stopped for a minimum of 5 days prior to the intervention
- Aspirin that is more than the maximum dose of 75 mg once daily
- Prosthetic heart valve, pacemaker, or any other implanted cardiac device

- Other malignant nodules or nodules with indeterminate cytology in either lobe
- Pre-existing vocal cord palsy

Any queries regarding eligibility should be discussed with the Chief Investigator (CI) via the RABBIT Trial office.

4.3. Co-enrolment

Participants in RABBIT may only participate in other non-interventional studies, such as observational or qualitative studies.

5. CONSENT

It is the responsibility of the Principal Investigator (PI) to obtain written informed consent for each participant prior to performing any trial related procedures. This task can be delegated by the PI to other appropriately qualified members of the local research team, if local practice allows and this responsibility has been documented in the RABBIT Site Signature and Delegation Log (SSDL).

Consent process

Potentially eligible patients will be identified at clinic appointments. A Participant Information Sheet (PIS) will be provided to facilitate the consent process. The PI or delegate will ensure that they adequately explain the aim of the trial, the trial intervention, and the anticipated benefits and potential hazards of taking part in the trial to the patient. They will also explain that participation is voluntary and that the patient is free to decide to take part and may withdraw from the trial at any time without having to provide a reason. The patient will be given sufficient time to read the PIS and to discuss their participation with others outside of the site research team. The patient will be given the opportunity to ask questions before signing and dating the latest version of the Informed Consent Form (ICF). If the participant then expresses an interest in participating in the trial, they will be asked to sign and date the latest version of the ICF. The PI or delegate will then sign and date the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF. In addition, the participant will be asked if they understand and to acknowledge that a copy of the signed ICF will be transferred to the trial team at BCTU for review.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant, version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

At each visit, the participant's willingness to continue in the trial will be ascertained and documented in the medical notes. Throughout the trial, the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's

continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue they will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Electronic copies of the PIS and ICF will be available from the Trial Office and will be printed or photocopied onto the headed paper of the local institution.

6. ENROLMENT, RANDOMISATION and BLINDING

6.1. Identification

Participants will be identified when attending for outpatient appointments (ear, nose and throat (ENT) surgery, endocrine surgery, or endocrinology). These will be either new or follow up appointments for patients found to have symptomatic thyroid nodular disease. The standard of care for patients referred with a symptomatic, previously unidentified thyroid nodule(s) is to undergo a physical examination including vocal cord mobility assessment in clinic, thyroid function testing, INR test (depending on unit), and then to be referred for a US (for the purpose of the trial this is classed as the initial US) and an FNAC should the nodule not be clearly benign, before being seen again in clinic with the results. Within each recruiting site, clinicians carrying out these clinics will identify potentially eligible patients (symptomatic thyroid nodule, deemed benign on the initial US and FNAC (if required), and fulfilling the radiological criteria as determined by an appropriately trained clinician) and contact the local research team. If the initial US deems the patient's thyroid gland/thyroid nodule is not potentially suitable for RFA then the patient does not progress with screening and enrolment.

6.2 Screening and enrolment

The local research clinician will discuss the trial with potentially eligible patients, and if agreeable they will be sent a PIS, and an appointment will be arranged to explain the study and obtain informed consent. Once consented, if any of the following standard of care investigations have not been carried out - vocal cord mobility assessment, thyroid function testing, INR test - these will be arranged and results will be reviewed against the eligibility criteria. Patients will then undergo a further US (for the purpose of the trial this is classed as the screening US) carried out by an RFA trained radiologist to ensure that nodule in question is suitable for RFA; if an FNAC has not already been performed as standard of care diagnostic work up, (for U2/TIRADS2 thyroid nodules) this will be carried out at the same sitting.

Details (including reason for ineligibility) of all patients approached about the trial by the clinical team will be recorded on the RABBIT Screening Log regardless of whether they were recruited to the trial or not. The RABBIT Screening Log will be completed online in the REDCAP annex (https://bctu-annex.redcap.bham.ac.uk/) . Screening data will be entered onto the Screening eCRF.

6.3 Randomisation

Randomisation will be provided by BCTU using a secure online system (available at https://bctu-redcap.bham.ac.uk). Unique log-in usernames will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the trial as detailed on the SSDL. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access the system using another person's login details. The online system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. In the rare event of the online system being unavailable, the local research team will contact the BCTU Trial Office (Mon-Fri between 9am and 5pm except for bank holidays, government guided closures, and UoB closed days) who will randomise the participant using an emergency paper backup, the details from which will later be added to the database.

6.4 Randomisation process

The RABBIT Randomisation electronic case report form (eCRF) will be available online to the investigators and can be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Form must be answered prior to a participant being randomised into the trial and a Trial Number being issued.

Following randomisation, a confirmatory e-mail will be sent to the local PI and the person who randomised the participant to the intervention. Participants will not be notified of the outcome of their randomisation until the baseline participant questionnaires have been completed.

The local research team should add the participant to the RABBIT Recruitment and Identification Log which links participants with their Trial Number. PIs must maintain this document securely and it must not be submitted to the RABBIT Trial Office. The RABBIT Recruitment and Identification Log should be held in strict confidence.

6.4.1 Randomisation method

Participants will be randomised at the level of the individual in a 1:1 ratio to either RFA or hemithyroidectomy.

A minimisation algorithm will be used within the randomisation system to ensure balance in the treatment allocations over the following variables:

- Centre where treatment is undertaken (as RFA and surgery are operator dependent)
- Solitary vs multiple unilateral vs multiple bilateral nodules (as multiple nodules are more difficult to treat)
- Nodule size: <20 cm^3 vs ≥20 cm^3 (as better outcomes are reported in smaller nodules)
- Gender that participant identifies as: male vs female vs non-binary vs other

To avoid the possibility of the intervention allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

6.5 Blinding

Due to the nature of the intervention, blinding is not possible in this trial.

7. TRIAL INTERVENTION

7.1. Trial intervention

After randomisation, the allocated intervention should take place within 6 months. Participants will be randomised to receive either: Hemithyroidectomy or RFA.

- **Hemithyroidectomy**
    - If the participant is randomised to the surgery arm, they will be listed for hemithyroidectomy in line with the local process. The hemithyroidectomy, including any pre-operative assessments and admission procedures, will be carried out as per the local SOP and guidelines.
- **RFA**
    - If the participant is randomised to the RFA arm, a request for the procedure will be made in line with local process. The procedure will be carried out by the appropriately trained and delegated clinician (on the SSDL), (see section 12.1). The procedure will be carried out as per the RABBIT RFA Manual taking into account any pre-existing local RFA guidance.
    - Further repeat RFA treatment will be at the discretion of the local PI, based on the clinical need of the participant. This should be documented on the Repeat RFA eCRF.

Details of the intervention will be documented in the Intervention eCRF by the local research team.

7.2. Drug interaction or contraindications

There are no prohibited medications or interventions other than those outlined and listed in the exclusion criteria.

7.3 Intervention modification or discontinuation

For patients undergoing surgery, withdrawal may occur at any point up to the point of surgery, and be due to patient choice, or the development of other significant medical conditions that are incompatible with surgery or will delay surgery significantly. Once surgery has begun, it is not expected that any procedures will be discontinued.

For those undergoing RFA, withdrawal may occur prior to the procedure for the reasons above. During the procedure, discontinuation may be due to patient wish, inability to achieve adequate anaesthesia, a large haematoma, skin burn, or any other complications and will be documented on the Intervention eCRF.

The reason for discontinuation will be documented in the Intervention eCRF. Any withdrawal or change of status will be documented in the Change of Status eCRF.

7.4 RFA generator supply and storage

Medical Radiofrequency Generators and probes will be provided by a UK accredited company in line with local policies on procurement.

Responsibility for ordering, delivery, storage, and PAT testing remains with the individual site as per local practice.

7.4.1 Intervention supplies

Sites will be provided with Medical Radiofrequency Generators and will have to purchase probes directly from the accredited supplier either individually (on a per participant basis) or in bulk if several RFA procedures are expected to be carried out in a short space of time. Each generator will come with a user manual.

7.4.2 Intervention recalls

The accredited supplier will be responsible for handling the recalls procedure. The site will be contacted by the accredited supplier in the event of any product recalls.

7.5 Adherence

Adherence to the allocated treatment will be measured by the treatment received by the participant. Those randomised to the RFA arm will be considered adherent if they undergo RFA within 6 months of randomisation and those randomised to the hemithyroidectomy arm are considered adherent if they undergo hemithyroidectomy within 6 months of randomisation.

8. OUTCOME MEASURES

8.1. Internal pilot outcomes

The success of the 6 month internal pilot will be based upon the ability to recruit, consent, and randomise patients, as well as the ability to open accredited sites. We aim to recruit 84 participants, and open 2 sites per month. The internal pilot will also enable us to address any issues that arise with regards adherence to the intervention.

Stop/Go Criteria

We have set criteria relating to the number of participants recruited, the number of sites activated and the recruitment rate per site (see Table 3 below):

• GO: progress to main trial; following the pilot phase we would still review trial processes to assess whether any changes could/need to be implemented to improve the trial.

• MODIFY: review the trial processes to identify implementable changes. This may include recruiting additional centres and/or retraining centres in trial pathways and procedures. We would discuss

with the trial oversight committees and funder about the need for a second internal pilot phase to verify resolution of issues, then if progress is satisfactory continue to the main trial.

• STOP: abandon the trial if the trial oversight committees and funder feel this is the appropriate course of action.

Progression criteria	Red	Amber	Green
Trial Recruitment % of pilot target (n=84)	<50% (i.e. <42 pts)	50-99% (i.e. 42 to 83 pts)	≥100% (i.e. ≥84 pts)
Average recruitment rate/site/month	<1	1.0-1.99	≥2
Number of sites opened	<6	6-11	≥12

Table 3: Internal pilot progression criteria

8.2 Main trial outcomes

8.2.1 Primary outcomes

- Goitre symptom score at 12 months post intervention- using the goitre domain of the ThyPRO tool

8.2.2 Secondary outcomes

8.2.2.1 Clinical

- Composite ThyPRO score (overall quality of life) at 12 months post intervention
- ThyPRO domain scores for: hyperthyroid symptoms, hypothyroid symptoms, eye symptoms, tiredness, cognition, anxiety, depressivity, emotional susceptibility, impaired social life, impaired daily life, impaired sex life and cosmetic complaints. All at 3, 12, 24 and 36 months post intervention.
- Incidence of complications within 3 months post intervention
- Incidence of hypothyroidism up to 36 months post intervention
- Incidence of temporary or permanent recurrent laryngeal nerve palsy at 12 months post intervention
- Percentage volume reduction in treated nodule(s) at 12 months post intervention (RFA arm only)
- Need for additional procedures related to the condition or treatment received up to 36 months post intervention
- Nodule recurrence at 36 months post intervention assessed by US (RFA arm only)
- Pain intensity (related to pre-existing pain levels and the procedure – measured using pain VAS) at immediately post-intervention, 3, 12, 24, and 36 months post intervention
- Related re-admission to hospital within 30 days of the initial trial intervention

8.2.2.2 Economic

- Cost effectiveness at 12 months

- Health related quality of life (using the EQ-5D-5L)
- Health resource usage (HRUQ)

8.2.3 Other

- Acceptability of RFA to patients (determined by take-up at screening)

9. TRIAL PROCEDURES

9.1. Schedule of assessments

Assessment	Screening	Baseline	Randomisation	Intervention	3M ± 2W	12M ± 8W	24M ± 8W	36M ± 8W
Eligibility check	x							
Informed consent	x							
Relevant medical history	x			x				
Vital signs	x			x				
Vocal cord mobility assessment	x				x	(x if needed)		
FNAC	x †‡							
Thyroid function tests	x *				x	x		x
INR test	x *							
US with report	X				(x RFA only)	(x RFA only)		(x RFA only)
Randomisation			x					
Weight				x	x	x		x
Height				x				
EQ-5D-5L and ThyPRO		x			x	x	x	x
Pain VAS		x		x	x	x	x	x
Intervention				x				
Pregnancy test (urine)	(x as required)			(x as required)				
Adverse events				x	x	x	x	x
Concomitant medications	x			x	x	x		x
HRUQ					x	x	x	x
Physical Examination					x	x		x

Table 4: Schedule of Assessments

**Performed post consent or within 6 months prior to consent if standard of care*

†If the nodule is classified as a U2 nodule, then 1 x Thy2 FNAC will be required. If the FNAC yields a Thy1 result, it will need to be repeated until the result is >Thy1.

‡ If the nodule is classified as a U3 nodule, 2 x FNACs which both yield a Thy2 result will be required

Intervention within 6 months post-randomisation. All follow up visits either ± 2 weeks/8 weeks post-intervention

9.2 Procedures

Eligibility check

Patients will have been identified as per section 6.1. Once a patient has been identified as potentially eligible, they will be screened using the data from the patient's existing medical records, as well as assessments which are conducted as part of standard of care. If the patient has had a previous US (initial US – section 6.1), an FNAC and vocal cord mobility assessment at any point, and thyroid function and INR within the past 6 months as part of standard of care tests, these data will be used as part of the screening assessments and documented on the Screening eCRF. The local PI, or delegated medically qualified clinician, will perform the final check and confirm eligibility against the full list of eligibility criteria and carry out any missing screening investigations. As described in section 6.2, a further US (screening US) will be carried out by an RFA trained radiologist to ensure suitability for RFA, and an FNAC carried out if not done before.

Informed consent

Please see section 5 for details of the informed consent process.

Relevant medical history

A medical history will be taken during the screening period to confirm eligibility and to capture any relevant conditions related to the thyroid and when these started or were diagnosed.

Vital signs

Vital signs including heart rate (beats per minute), respiration rate (breaths per minute) and blood pressure (mmHg), will be collected at the screening and intervention visits.

Vocal cord mobility assessment

The vocal cord mobility assessment will be performed post consent if not already done as part of standard of care assessments prior to intervention. A vocal cord mobility assessment should then be performed for all participants at the 3 months follow up visit. If this shows impaired vocal cord mobility, reflecting recurrent laryngeal nerve injury, it should be repeated at the 12 months follow up visit. No further vocal cord assessments will be required thereafter.

Fine Needle Aspiration Cytology (FNAC)

The FNAC should be completed as part of standard of care assessments to confirm the benign nature of the thyroid for continuation of entry into the trial. An appropriately trained cytopathologist should review the FNAC to confirm the thyroid is benign.

If the nodule is classified as a **U2 nodule, then 1 x Thy2 FNAC result is required** for participation in the trial. If the FNAC yields a Thy1 or Thy3a result, a repeat will be carried out to determine if the nodule is Thy2. Should the repeat FNAC not yield a Thy2 result, the patient will be ineligible for the trial.

If the nodule is classified as a **U3 nodule, 2 x FNACs which both yield a Thy2 result** will be required as standard of care. A maximum of 2 FNACs will be carried out, should 2 x Thy2 results not be obtained then the patient will be ineligible.

If the **nodule fails to meet these criteria**, the participant is not eligible. Screening can be stopped and no further tests should be conducted as part of the trial. Any further care for this participant should be continued by the clinical team as per local processes. All FNACs performed should be documented on the RABBIT FNAC eCRF.

Thyroid Function Tests

Thyroid function tests will be performed post consent if not already performed as part of standard of care in the last 6 months. The thyroid function tests must include TSH and Free T4. At screening, the TSH result must be less than the upper limit of the local reference range, and greater than 0.1mIU/L. If the TSH result is greater than 0.1mIU/L and less than the lower limit of the local reference range (thus considered to be abnormal), then a Free T4 test should be performed, and this must be within the local reference range for the participant to be eligible for entry into the trial. If the results do not meet these criteria, the participant is not eligible. Screening should be stopped, and no further tests may be conducted as part of the trial. Thyroid function tests, including TSH and Free T4 should be performed at the 3 months, 12 months and 36 months follow up visits. Any abnormal results within the safety reporting period should be recorded as an adverse event (AE) on the Follow up eCRFs.

International Normalised Ratio

The INR will be performed post consent if not already performed as part of standard of care. The INR result should be less than or equal to 1.5 for the participant to be eligible for entry into the trial. If this result does not meet this criterion, the participant is not eligible. Screening should be stopped and no further tests should be conducted as part of the trial.

Randomisation

Please see section 6.3 for details of randomisation. The participant must not be randomised until they have completed the baseline questionnaires.

Height and Weight

Height and weight should be measured for the BMI calculation at the intervention, and thereafter, the weight will be measured at the 3 months, 12 months and 36 months follow up visits.

Participant questionnaires (EQ-5D-5L, ThyPRO, Pain VAS, HRUQ)

The baseline questionnaires must not be completed until the local PI has confirmed eligibility. Participants should be asked if they are happy to complete the questionnaires electronically and if so, they will be e-mailed the questionnaires. For participants who do not wish to complete questionnaires electronically, paper questionnaires will be posted out by the RABBIT Trial Office and participants will be asked to return them to the RABBIT Trial Office in a pre-paid envelope once completed.

EQ-5D-5L

The EQ-5D-5L questionnaire is a self-assessed health related quality of life questionnaire.

ThyPRO

The ThyPRO tool is the disease specific outcomes questionnaire.

Both the EQ-5D-5L and ThyPRO will be completed at baseline, 3 months, 12 months, 24 months, and 36 months post intervention.

Pain VAS

Participants will be asked to complete the pain VAS to measure pain intensity. This will be completed at baseline and after the intervention: for the RFA arm, the pain VAS will be completed post-procedure; for the surgery arm, the pain VAS will be completed post-surgery or on the day of discharge. This will be completed again at 3 months, 12 months, 24 months, and 36 months post intervention in both arms of the study.

Health Resource Usage Questionnaire (HRUQ)

The HRUQ will be used for the assessment of cost effectiveness between both interventions. This questionnaire will be completed at each follow up time point to include 3 months, 12 months, 24 months, and 36 months post intervention.

Please see table 14 for information.

Intervention

Please see section 7 and the RFA Manual for details and guidance for the allocated intervention.

Pregnancy test

For participants assigned female at birth and of child bearing potential (determined at the local clinician's discretion), a urine pregnancy test will be performed at screening. If this results in a positive test result, the participant will be a screen fail, and this should be documented on the Screening eCRF. If the participant is eligible and is randomised, the pregnancy test should be repeated prior to the intervention. A positive test will result in withdrawal from the intervention. The participant will remain in the trial and be followed up as per the protocol for all other trial investigations. This should be documented in the RABBIT Change of Status Form.

Adverse events/serious adverse events

Targeted AEs will be collected throughout follow up and, reported at the 3 months, 12 months, and 36 months follow up visits. Expediting of serious adverse events (SAEs) will be dependent on the nature of the SAE. See section 10 for further details of safety reporting.

Concomitant medications

Information about current medications will also be collected at the screening visit to confirm eligibility.

Targeted concomitant medications and medications prescribed post intervention will be collected upon discharge and at 3 months, 12 months, and 36 months follow up visits. These will include any thyroid hormone replacement medications and analgesia.

Physical Examination

The physical examination of the scar should take place at the 3 months, 12 months, and 36 months follow up visits.

US with report (RFA arm only)

For participants who are randomised to the RFA arm, US will be carried out at the 3 months, 12 months, and 36 months follow up visits. The results from the US will be documented on the 'RABBIT Ultrasound Form'.

9.3 Withdrawal and changes in levels of participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation at all visits. Participants should be aware from the beginning that they can freely withdraw (cease to participate) from the trial at any time without having to provide a reason. A participant may wish to cease to participate in a *particular* aspect of the trial.

Participants found to be ineligible post randomisation should be followed up according to all trial processes and will still have their data analysed unless they explicitly change their level of participation. This includes participants who are assigned female at birth who are found to have a positive pregnancy test on the day of the intervention, or participants who have started a medication listed on the exclusion criteria after being randomised.

The changes in levels of participation within the trial are categorised in the following ways:

No trial intervention: The participant would no longer like to receive the trial intervention but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e., the participant has agreed that data can be collected and used in the trial analysis).

No trial related follow-up: The participant does not wish to attend trial visits in accordance with the schedule of assessments, but is willing to be followed up at standard clinic visits.

No further data collection: The participant is not willing to be followed up in any way for the purposes of the trial AND does not wish for any further data to be collected (i.e., only data collected prior to any changes of levels in participation can be used in the trial analysis).

The details of changes of levels in participation within trial (date, reason, and category of status change) should be clearly documented in the source documents and reported on the RABBIT Change of Status Form.

10. ADVERSE EVENT REPORTING

10.1. Definitions

The recording and reporting of AEs will be in accordance with the Principles of Good Clinical Practice (GCP) as defined by the UK Policy Framework for Health and Social Care (2017) and the requirements of the Health Research Authority (HRA). It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity, seriousness and causality (relatedness) with reference to the RABBIT Protocol.

Definitions of different types of AEs are listed in table 5.

Severity Definitions	Mild	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae.
	Moderate	A sign or symptom, which interferes with the participant's usual activity.
	Severe	Incapacity with inability to do work or perform usual activities.
Types of Adverse Events		
Adverse Event	AE	Any untoward medical occurrence in a participant participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event	RE	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly/ birth defect • Or is otherwise considered medically significant by the Investigator**
Unexpected Event	UE	The type of event that is not listed in the protocol as an expected occurrence.

Related and Unexpected Serious Adverse Event	N/A	A SAE that meets both the definition of a Related and Unexpected Event.

Table 5: Adverse event reporting definitions

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

10.2. AE/SAE reporting period

The reporting period for AEs and SAEs in RABBIT will be from the day of the intervention until the end of the trial follow-up period.

10.3. Adverse events in RABBIT

Participants that meet the eligibility criteria for the RABBIT Trial will likely experience numerous AEs. As these events are well characterised, it is highly unlikely that these AEs will reveal any new safety information relating to the trial intervention, RFA. Due to this, only targeted events that meet the definition of an AE, but not an SAE (see table 6) will be required to be reported to the trial team on the appropriate Intervention or Follow up eCRF. These AEs should also be recorded as per local practice within the medical record. Please note this includes abnormal thyroid function tests.

Expected AE	Process
Haematoma *±	Document in Intervention or Follow up eCRF
Wound Infection*±	
Scar/healing problems; keloid, hypertrophy*	
Wound dehiscence*	
Chest infection*	
Oral/oropharyngeal injury*	
Failure to intubate/ventilate*	
Failure to anaesthetise (general* or local±)	
Urinary retention*	
Post-operative nausea and vomiting*	
Abscess*	
Seroma*	
Hypothyroidism*±	
Skin burn±	

Abnormal thyroid function tests±	

Table 6: AEs that require reporting. * Related to hemithyroidectomy ± Related to RFA

10.4. Serious Adverse Events in RABBIT

This trial employs a targeted approach to SAE reporting and therefore we have outlined anticipated SAEs that do not require reporting and anticipated SAEs that do not require expedited reporting. For all SAEs, the PI or delegate must do one of the following:

- **Record safety reporting-exempt SAEs** in the medical notes but not report them to the Trial Office on an SAE form as per Table 7.
- **Report SAEs in a non-expedited manner** to the Trial Office for the pre-defined subset of SAEs as per Table 8.
- **Report SAEs in an expedited manner** (within 24 hours of the site research team becoming aware of the event) to the Trial Office for SAEs not covered by the above 2 categories as per Table 9.

10.4.1 Serious Adverse Events not requiring reporting to the Trial Office

Several events that meet the definition of an SAE will not require reporting on the trials dedicated SAE form. If any of the events outlined below in table 7 occur during an individual's participation, from the date that the trial intervention started through to the end of follow-up, reporting the event on a SAE form is not required as the SAE is not considered to be critical to evaluations of the safety of the trial.

Expected SAE	Process
SAEs relating to a pre-existing medical condition or those that have occurred which are unrelated to either intervention: hemithyroidectomy or RFA, or the condition under investigation	Document in medical notes only

Table 7: SAEs that do not require reporting

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, throughout the participant's time on trial, including follow-up, but for trial purposes these events do not require reporting on the SAE Form. Such events are 'safety reporting exempt'.

10.4.2 Serious Adverse Events requiring non-expedited reporting to the Trial Office

Where the safety profile is well established, the causal relationship between the intervention (or the participant's underlying condition), and the SAE, may be known. Such events should still be recorded by the site research team in the participant's medical notes and reported to the RABBIT Trial Office, but it does not require expedited reporting (immediately on the site becoming aware of the event) since the assessment of expectedness for the specified event has been pre-defined. The timeline for reporting non-expedited SAEs to BCTU is within 30 days. These SAEs are listed in Table 8 below.

Non-expedited SAE	Process
Unplanned Hospital admissions	Report on SAE eCRF within 30 days of the site becoming aware.
Death – The cause of which is unrelated to intervention	
Recurrent laryngeal nerve injury*±	
Need for reoperation as a result of haematoma*	
Need for reoperation as a result of wound infection/abscess/seroma*	
Pulmonary embolism or deep vein thrombosis*	
Pneumothorax	
Myocardial Infarction	
Prolongation of post intervention stay in hospital lasting more than 48 hours* or more than 12 hours ±	
Horner's syndrome±	

Table 8: SAEs requiring non-expedited reporting in RABBIT *Related to hemithyroidectomy ± Related to RFA

10.4.3 Serious Adverse Events requiring expedited reporting to the Trial Office

All SAEs not listed in Sections 10.4.1 and 10.4.2 must be reported to the RABBIT Trial Office on the RABBIT SAE Form within 24 hours of the site research team becoming aware of the event.

Examples of SAEs that would require expedited reporting can be found in the table 10 below.

Expedited SAE	Process
Tracheal Injury*	Report on SAE Form eCRF within 24 hours of the site becoming aware of the event.
Oesophageal Injury*±	
Carotid Sheath Injury*±	
Brachial plexus injury*±	
Malignant hyperpyrexia*	
Need for surgical intervention post procedure±	
Nodule rupture±	
Death – as a result of the intervention*±	
Other expedited SAE*±	

Table 9: Examples of SAEs that require expedited reporting in RABBIT *Related to hemithyroidectomy ± Related to RFA

10.5 SAE Reporting process

On becoming aware that a participant has experienced an SAE which requires reporting on an SAE form, the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the RABBIT Trial Office.

To report an SAE to the RABBIT Trial Office, the PI or medically qualified delegate must complete, date, and sign the RABBIT SAE Form on the database. The form will be completed on the study database as soon as possible and no later than 24 hours or 30 days after the site first becoming aware of the event in accordance with the timelines given in Section 10.4.2 and 10.4.3 depending on the nature of the SAE.

To report an SAE, please complete the SAE Form on https://bctu-redcap.bham.ac.uk

On receipt of an SAE eCRF, the database will allocate each SAE a unique reference number and notify the site via email as proof of receipt.

If the site has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE identification number within 1 working day of reporting, the site should contact the Trial Office. The site and the Trial Office should ensure that the SAE reference number is quoted on all correspondence regarding the SAE. Where an SAE Form has been completed by someone other than the PI initially, the original SAE form must be countersigned by the PI to confirm agreement with the causality and severity assessments.

10.5.1 Assessment of causality of an SAE

When completing the SAE form, the PI (or, throughout this section, a medically qualified delegate) will be asked to define the nature of the seriousness and causality (relatedness; see Table 10) of the event.

In defining the causality the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per Table 10, all events considered to be ‘possibly’, ‘probably’, or ‘definitely’ related to the intervention will be reported by the RABBIT Trial Office as ‘related’; all events considered at site to

be ‘unlikely’ or ‘unrelated’ to the intervention will be reported by the RABBIT Trial Office as ‘unrelated’.

The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the participant’s clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

Table 10: Categories of causality

On receipt of an SAE Form, the CI or delegate(s) will independently* review the causality of the SAE. An SAE judged by the PI or CI or delegate(s) to have a reasonable causal relationship (“Related” as per Table 10) with the intervention will be regarded as a related SAE (i.e., SAR). The severity and causality assessment given by the PI will not be downgraded by the CI or delegate(s). If the CI or delegate(s) disagrees with the PI’s causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report.

*Where the CI is also the reporting PI an independent clinical causality review will be performed.

10.5.2 Assessment of expectedness of an SAE by the CI

The CI or delegate(s) will also assess all related SAEs for expectedness with reference to the criteria in Table 11.

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the relevant safety information. See section 10.3 for expected events.

Unexpected	An adverse event that is not consistent with known information about the trial related procedures.

Table 11: Categories of expectedness

If the event is unexpected (i.e., it is not defined in the protocol as an expected event) it will be classified as a related and unexpected SAE.

The CI will undertake review of all SAEs and may request further information from the clinical team at site for any given event(s) to assist in this.

10.5.3 Provision of SAE follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the Trial Office. Where significant new information is reported, the PI (or medically qualified delegate) should also consider review and update of relatedness and causality as applicable.

10.6. Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings.

The Trial Office will report all events categorised as Unexpected and Related SAEs to the REC and RGT within 15 days of being notified.

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to the PIs. A copy of any such correspondence should be filed in the ISF and Trial Master File (TMF).

10.7. Urgent Safety Measures

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the reason why they have been taken.

10.8. Follow-up of pregnancy outcomes for potential SAEs

Known pregnancy at the time of randomisation is an exclusion criterion, however, in the unlikely event that a participant becomes pregnant prior to delivery of the intervention, the intervention will not be administered. A pregnancy test at the intervention visit, prior to delivery of the intervention is part of standard of care. This result will be recorded on the Intervention eCRF. There is no identified risk of congenital anomalies or birth defects in the offspring of participants as a result of their participation in the trial and therefore there is no requirement for a pregnancy notification form or any subsequent follow up.

11. DATA HANDLING AND RECORD KEEPING

11.1.Source data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained.

Source data is kept as part of the participants' medical notes generated and maintained at site. In addition, for this trial, participant reported outcome measures (PROMs) will be collected; the source data will be stored electronically where participants have completed electronic records. For PROMs completed on paper, this will be considered the source data. The list within table 12 is not exhaustive.

Data	**Source**
Participant Reported Outcomes Questionnaires	The original participant completed PRO questionnaires will be the source data and these will be stored either: > Electronically on the eCRF, if the participant has completed them online, OR > At the BCTU Trial office, if they have been completed on paper and returned to the trial office. The information will be transcribed onto the eCRF.
Lab results	The original lab report (which may be electronic) is the source and will be kept and maintained, in line with normal local practice.
Vital signs	The routine clinic observations at various time points will be available from the medical notes/electronic participant record system, which will be kept and maintained in line with normal local practice. The medical notes/electronic participant record system is the source.
Imaging	The source is the original imaging usually as an electronic file. Data may be supplied to the Trials Office as an interpretation of the imaging provided on the eCRF.
Clinical event data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of

	clinic (e.g., phone calls), must be documented in the source documents.
Recruitment	The original record of the randomisation is the source. It is held on BCTU servers as part of the randomisation and data entry system.
Change of status	Where a participant expresses a wish to change their level of participation, the conversation must be recorded in the medical records and this will constitute the source data.

Table 12: Source data in RABBIT

11.2. Case Report Form (CRF) completion

The eCRFs will be completed for each individual participant, and these will be electronic with the exception of the paper questionnaires which a portion of participants may complete and return to the RABBIT Trial Office.

The list of eCRFs will include but will not be limited to the following forms (see Table 13).

Form Name	**Schedule for submission**
Screening CRF	Post consent and prior to randomisation
Randomisation CRF	At the point of randomisation
Intervention CRF	Post intervention or upon discharge from hospital
Follow up CRFs including participant reported outcome measures and any AEs (within reporting period)	As soon as possible after each follow-up assessment time point.
Serious Adverse Event CRF	If expedited: completed within 24 hours of site research team becoming aware of event If non-expedited: completed within 30 days of site research team becoming aware of event
Change of status CRF	As soon as possible after the point of reduced participation, site becoming aware of pregnancy, withdrawal or death
Ultrasound CRF	As soon as possible after the US

Table 13: CRFs in RABBIT

In all cases it remains the responsibility of the PI to ensure that the eCRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the PI or delegate. The SSDL will identify all those personnel with responsibilities for data collection.

The delegated staff completing the eCRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by the date the eCRF data was entered.

Data reported on each eCRF will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete eCRFs will be trained to adhere to eCRF completion guidelines.

The following guidance applies to data and partial data:

- Only eCRFs within the RABBIT Redcap database should be used.
- Original completed PRO questionnaires or true copies should be sent to the Trial Office with copies filed in the ISF.
- Rounding conventions – rounding should be to the nearest whole number: If the number you are rounding is followed by 5, 6, 7, 8, or 9, round the number up. **Example**: 3.8 rounded to the nearest whole number is 4. If the number you are rounding is followed by 1, 2, 3 or 4, round the number down. **Example**: 3.4 rounded to the nearest whole number is 3
- Trial-specific interpretation of data fields – where guidance is needed additional information will be supplied
- Entry requirements for concomitant medications (generic or brand names) – generic names should be used where possible
- Missing/incomplete data – should be clearly indicated – all blank fields will be queried by the Trial Office
- Repeat laboratory tests – the data used to inform clinical decisions should always be supplied. If a test is repeated it is either to confirm or clarify a previous reading. Confirmatory tests should use the original test values.
- Protocol and GCP non-compliances should be reported to the Trial Office on discovery.

On completion of a trial visit, the research nurse or delegated member of the RABBIT team at the site will use all of the source data (for example participant notes, trial specific worksheets or forms) and transcribe the data captured at the visit onto the database.

The PROMs questionnaires that are completed electronically by the participant will automatically be transcribed onto the eCRF.

11.3. Participant completed questionnaires

Table 14 below shows how participants will complete various questionnaires at different time points.

Timepoint	Baseline	Post-procedure	3m	12m	24m	36m
	In between the screening and randomisation visits. Questionnaires must be completed prior to participant being randomised.	RFA arm: Post-procedure. Surgery arm: Post-surgery or on the day of discharge.	3 months post procedure	12 months post procedure	24 months post procedure	36 months post procedure
Location	Remote	In clinic	Remote	Remote	Remote	Remote
ThyPro	X		X	X	X	X

EQ-5D-5L	X		X	X	X	X
Pain VAS	X	X	X	X	X	X
HRUQ			X	X	X	X

Table 14: Completion of participant questionnaires

Remote completion

Participant completed questionnaires should be completed electronically where possible. However, the participant's preferred method for completing questionnaires will be asked at screening, and contact details for sending questionnaires will be obtained. The participant will be e-mailed or posted the questionnaire to complete when these are not being completed at the site (i.e. remote).

In clinic completion

Where the participants will be completing participant questionnaires in clinic e.g. Pain VAS post-procedure), these will be completed on paper and the site staff will transcribe the responses onto the eCRF.

- Entries should be made in dark ink and must be legible.
- Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated.
- Time format – all times should be in accordance with the 24hr clock

Where questionnaires are not returned, BCTU will make two attempts via post or e-mail reminders to retrieve completed questionnaires. Sites may also be requested to make at least one attempt to contact the participant to retrieve the completed questionnaires. All attempts should ideally be made within the specified time after the visit as stated in the schedule of events – table 4 (eg ±2 weeks or ±8 weeks).

11.4.Data Management

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan and include the processes of data entry and data queries and self-evident corrections on trial data. Data entry will be completed by sites via a BCTU-managed trial database, however, questionnaires returned to the Trial Office will be entered on the database by a member of the trial team at the Trial Office. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries will be raised using data clarification forms (DCFs) via the trial database, with the expectation that these queries will be completed by the site (ideally) within 30 days of receipt. Overdue data entry and data queries will be requested on a monthly basis.

11.5.Self-evident corrections

Self-evident corrections will only be permitted:

For **contingent fields:** When a response to a question determines, to a degree, the response required by a second question, then conflicts in the responses can be resolved by the data entry

clerk. E.g., Has the person had procedure “x”? If yes, state type. If the response to the first question is “no”, yet the type of procedure is stated, it is self-evidently true that the initial response was incorrect.

For **changes to administrative notes and reference numbers:** when new information becomes available such that a reference number does not accurately reflect the sequence of eCRFs received e.g., an SAE form is received for an incident which occurred prior to an already reported incident, then it is appropriate to change the reference number provided no DCFs have been raised using the original number. Similarly, any notes relating to the participant care which have an impact on the administration process, but not the data fields themselves, can be changed as appropriate.

11.6.Data security

The UoB has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The BCTU has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.

Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls of non-identifiable data.

Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.

System management: the system will be developed by the Programming Team at the Trial Office, and will be implemented and maintained by the Programming Team.

System design: the system will comprise of a database and a data entry application, restricted access, encryption in transit and role-based security controls.

Operational processes: the data will be processed and stored within BCTU.

System audit: The system will benefit from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic IT risk assessment

Data Protection Registration: UoB’s Data Protection Registration number is Z6195856.

11.7. Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g., signed ICFs, Investigator Site Files, participants’ hospital notes, copies of eCRFs) at their site are securely retained for the contractual period. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU Director or their delegate.

The TMF will be stored at BCTU for at least 3 years after the end of the trial. Long-term off site data archiving facilities will be considered for storage after this time; data will be stored securely and

confidentially for at least 10 years. BCTU has standard processes for both hard copy and computer database legacy archiving.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Site set-up and initiation

All PIs will be asked to sign the necessary agreements including a SSDL between the PI and the RABBIT Trial Office and supply a current CV and GCP certificate. All members of the site research team are required to sign the SSDL, which details which tasks have been delegated to them by the PI. The SSDL should be kept up to date by the PI. It is the PI's responsibility to inform the RABBIT Trial Office of any changes in the site research team.

Alongside the RABBIT trial training, sites that do not currently perform thyroid RFA will need to undertake training with an established RFA equipment provider before RFA can be performed within the trial.

There are mandatory requirements in the training pathway to complete before RFA can be performed in the RABBIT trial. These are:

1. Completion of online training videos
2. Visiting an established RFA proctoring site to observe first hand thyroid RFA and practical overview of RFA equipment with proctor and industry liaison
3. RFA phantom model training at the local site to establish local procedures and identify potential issues
4. On site proctoring by an experienced RFA practitioner and industry liaison for their first trial participant, and further participants if deemed necessary by the proctor or delegated clinician

Clinicians who have had little or no experience in RFA will be expected to undergo steps 1 to 3 before undertaking step 4 and performing the procedure on trial participants.

Clinicians who are already familiar with the RFA procedure, but are not currently performing this on the thyroid, will be required to complete steps 3 and 4 in the training pathway.

Those clinicians who are already authorised to carry out thyroid RFA at their Trust will be exempt from following the mandated training pathway/steps. However, the training materials will be available to clinicians should they wish to access them.

Prior to commencing recruitment, each site will undergo a process of site initiation, either a meeting or a video-conference meeting, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

12.2.Monitoring

The central and on-site monitoring requirements for this trial have been developed in conjunction with the trial specific risk assessment and are documented in the trial specific monitoring plan.

12.2.1. On-site monitoring

For this trial, all sites will be monitored in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the RABBIT Trial Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered. PIs and site research teams will allow the RABBIT trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff.

12.2.2. Central monitoring

The Trial Office will check received ICFs and eCRFs for compliance with the protocol, data consistency, missing data and timing at a frequency and intensity determined by the Data Management Plan. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies. Audit and inspection

12.3. Audit and Inspections

The PI will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site and provide direct access to source data/documents. The PI will comply with these visits and any required follow-up. Sites are also requested to notify the RABBIT Trial Office of any relevant inspections or local audits.

12.4. Protocol Deviations

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the RABBIT trial team as these occur. Significant deviations from the protocol which are found to frequently recur are not acceptable; these will require immediate action and could potentially be classified as a serious breach.

12.5. Notification of Serious Breaches

A serious breach is defined as a breach that is likely to affect to a significant degree the safety or physical or mental integrity of the participants, or the scientific value of the project. The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or of the protocol relating to that trial. Sites are therefore requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware of them. Where the Trial Office is investigating whether or not a serious breach has occurred, sites are also requested to co-operate with the RABBIT Trial Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment.

13. END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture including resolution of DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. The RABBIT Trial Office will notify the REC and the Sponsor within 90 days of the end of trial. Where the trial has terminated early, the RABBIT Trial Office will notify the REC within 15 days of the end of trial. The RABBIT Trial Office will provide the REC and the Sponsor with a summary of the clinical trial report within 12 months of the end of trial.

14. STATISTICAL CONSIDERATIONS

14.1. Sample size

The ThyPRO tool assesses 13 different domains relating to patient reported outcomes measures in patients with benign thyroid disease including goitre symptoms. It also provides an overall composite score summarising the effect on QoL (30). Assuming a 1-sided significance level of 2.5% and a standard deviation of 21 (30) for patients with non-toxic goitre with a non-inferiority margin of 6.8 (Minimum Clinically Important Change (MCIC) from (42)) we will need to recruit 201 participants in each of the RFA and the surgery groups (402 in total) to have 90% power to determine whether the results in the RFA group were non-inferior to those in the surgery group. Assuming a dropout/loss to follow-up rate of 10%, the study will need to recruit 448 participants (224 in each arm). A non-inferiority margin of 6.8 points was selected based on previous validated studies and clinical judgment, and was determined to be an appropriate threshold of MCIC using the ThyPRO goitre domain.

14.2 Analysis of outcomes

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of the planned analyses is given below.

The primary comparison groups will be composed of those randomised to RFA versus those randomised to hemithyroidectomy. In the first instance, all analyses will be based on the intention to treat principle (ITT), i.e., all participants will be analysed in the intervention group to which they were randomised irrespective of adherence to randomised intervention or protocol deviations. A sensitivity analysis on the per-protocol population will also be conducted for the primary outcome. The ITT analysis will ensure a comparison that maintains the rigor of randomisation but could risk providing results that are biased towards non-inferiority and the per-protocol analysis (as a sensitivity analysis) will provide results that minimise this risk (see Section 14.2.4). For all outcome measures, appropriate summary statistics will be presented by group (e.g. proportions/percentages, mean/standard deviation or median/interquartile range). All outcomes will be presented with point estimates (e.g. relative risks, incident rate ratios, hazard ratios, mean differences) and confidence intervals. Where possible intervention effects will be adjusted for the minimisation variables (listed in Section 6.4.1) along with baseline Goitre symptom score. Due to the large number of secondary

outcomes, multiple comparisons will be adjusted for through presenting 99% confidence intervals (instead of 95%) for all secondary outcomes.

14.2.1. Primary outcome(s)

The primary outcome is the Goitre symptom score (from the Goitre domain of the ThyPRO tool) at 12 months post intervention. This domain consists of 11 questions with a total transformed score that ranges from 0-100 where 100 indicates the worst symptoms due to thyroid swelling. Linear regression methods will be used if the model residuals are sufficiently normally distributed (or where data can be suitably transformed), to calculate an adjusted mean difference and 95% confidence interval, adjusting for the minimisation variables listed in Section 6.4.1 alongside baseline Goitre symptom score. A p-value will not be presented for the primary outcome, as non-inferiority will be assessed based on the upper limit of the 95% CI.

14.2.2. Secondary outcomes

All secondary outcomes will be analysed using a superiority framework.

Continuous secondary outcomes (e.g. pain intensity) will be analysed using linear regression models if the outcome is sufficiently normally distributed (or where the data can be suitable transformed) and results presented as differences in means with 99% confidence intervals. For skewed continuous outcomes, unadjusted median differences and 99% confidence intervals will be presented.

Binary secondary outcomes (e.g. readmission to hospital) will be presented as number and percentage. A log-binomial regression model will be used to calculate the adjusted relative risk and 99% confidence interval. The adjusted absolute risk difference and 99% confidence interval between groups will also be reported using a binomial model with an identity link.

Secondary outcomes in the RFA arm only (e.g. percentage volume reduction in treated nodule at 12 months) will be summarised as a mean (for continuous outcomes) or proportion (for binary outcomes) with a 99% CI around this estimate.

14.2.3. Planned subgroup analyses

Subgroup analyses will be limited to the same variables used in the minimisation algorithm (except centre) (see Section 0) and performed on the primary outcome only. The effects of these subgroups will be examined by including an intervention group by subgroup interaction parameter in the regression model, which will be presented alongside the effect estimate and 95% confidence interval within subgroups. The results of subgroup analyses will be treated with caution and will be used for the purposes of hypothesis generation only.

14.2.4. Missing data and sensitivity analyses

Every attempt will be made to collect full follow-up data on all study participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of risk. This will include imputing missing data using a multiple imputation approach. Further sensitivity analysis will include a per protocol analysis, which will allow a robust evaluation of the non-inferiority hypothesis.

Full details will be included in the Statistical Analysis Plan.

14.3.Planned final analyses

The primary analysis for the trial will occur once all participants have completed the 36 months assessment and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis. This analysis will include data items up to and including the 36 months assessment and no further.

15. HEALTH ECONOMICS

A separate Health Economics Analysis Plan will be produced and will provide a more comprehensive description of the planned analyses. A brief outline of these analyses is given below.

15.1.Within-trial economic evaluation

The economic evaluation will explore the relative cost-effectiveness of RFA compared with hemithyroidectomy, in the treatment of benign thyroid nodules. This will take the form of an incremental cost-utility analysis to estimate cost per quality adjusted life year (QALY) over 3 years follow-up, using patient level data on costs and outcomes from the trial. A cost-consequence analysis will initially be reported, describing all the important results relating to costs and consequences. The base-case analysis will be performed according to the intention-to-treat analysis from an NHS and personal social services (PSS) perspective. A broader costing perspective will be considered in a sensitivity analysis, taking into account NHS/PSS costs and productivity costs associated with time off work. Costs will be collected within the trial to determine the cost of the treatments and other benign thyroid nodule healthcare utilisation. Resource use information on benign thyroid will be collected via questionnaires within the trial on primary care consultations (general practitioners and practice nurses), and other health professionals in the GP practice, secondary care consultations (e.g., hospital consultants, speech therapists), hospital-based procedures (investigations, surgeries, additional radiofrequency ablation), nature and length of stay from SAEs. Resource use data will distinguish between private and public NHS use. Unit cost data will be obtained from standard sources including the British National Formulary **(52)**, Unit costs of Health and Social care **(53)** and NHS reference costs **(54)**. Data on broader costs will also be collected, related to both out of pocket costs and time off work to enable calculation of productivity losses, allowing analysis from a societal perspective. The average wage rate will be identified, and the human capital approach used to estimate productivity costs **(55)**. QALYs will be generated using patient level responses to the EQ-5D-5L obtained at baseline, 3, 12, 24 and 36 months.

QALYs will be calculated from the EQ-5D-5L data using the area under the curve approach, with regression-based adjustment for baseline EQ-5D-5L score **(56, 57)**. Unit costs will be applied to the healthcare resource items, and mean resource use and total costs calculated for all trial participants. Cost data is normally skewed, and where appropriate a non-parametric comparison of means (using bootstrapping) will be undertaken. Following best practice guidelines, missingness mechanisms will be explored, and multiple imputation methods used for EQ-5D-5L and cost missing data where appropriate to avoid biases associated with complete-case analyses **(58)**. Incremental cost-utility analysis will then be undertaken to estimate the incremental cost per QALY gained, adjusting for baseline covariates. Results will be presented in incremental cost-effectiveness ratios (ICERs) using ICER plots and cost-effectiveness acceptability curves to represent the probability of the intervention being cost-effective at different willingness to pay thresholds. Costs and outcomes arising during the trial will be discounted reflecting the 3-year time horizon. The robustness of the results will be explored using sensitivity analysis. This will explore uncertainties in the trial-based data itself, the methods employed to analyse the data and the generalisability of the results to other settings. Cost-effectiveness acceptability curves will also be produced to reflect the probability that the intervention will be cost effective at different cost per QALY willingness to pay thresholds.

15.2.Model-based economic evaluation

Extensive economic modelling using decision modelling will be carried out to extend the time horizon and decision context beyond 3 years follow up, using outcome data from routine data where appropriate. The model in the form of a Markov model will extrapolate costs and QALYs over a lifetime time horizon to calculate the long-term cost-effectiveness (cost per QALY) of the intervention, from an NHS perspective. In addition to trial and routine data, the model will be populated with data from existing literature on the natural history of the condition, associated risks with the intervention, and quality of life, national data on all-cause mortality and stakeholder consultations where appropriate. Parameter uncertainty in the decision-analytic model will be explored using deterministic and probabilistic sensitivity analysis. Longer-term costs and consequences will be discounted to present values using discount rates recommended for health technology appraisal in the UK (current discount rate: 3.5%). Cost-effectiveness planes and cost-effectiveness acceptability curves will be presented to show the probability that the intervention is cost-effective at different cost/QALY thresholds.

16. SUB-STUDIES

There are no sub-studies within this trial.

17. TRIAL ORGANISATIONAL STRUCTURE

17.1. Sponsor

The Sponsor for this trial is UoB.

17.2. Coordinating centre

The trial coordinating centre (RABBIT Trial Office) is the BCTU, based at UoB.

17.3. Trial Management Group

The Trial Management Group (TMG) comprises individuals responsible for the day-to-day management of the trial: the CI, the Co-Lead, statisticians, trial management team leader, trial manager and data manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet sufficiently frequently to fulfil its function.

17.4. Co-investigator group

The Co-investigator group, an extended TMG, will comprise all members of the co-applicant group and the members of the TMG to review progress, troubleshoot and plan strategically.

17.5. Trial Steering Committee

A Trial Steering Committee (TSC), comprising independent and non-independent members, will be established for the RABBIT trial and will meet as required depending on the needs of the trial. Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the role of the TSC is to provide oversight of the trial. The TSC will monitor trial progress and conduct, and provide advice on scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC. The TSC will operate in accordance with a trial specific TSC Charter.

17.6. Data Monitoring Committee

The role of the independent DMC is to monitor the trial data and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and (where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence.

The DMC will operate in accordance with a trial specific DMC Charter which will define the membership, roles and responsibilities of the DMC. The DMC will meet at least annually as a minimum. Additional meetings may be called if needed e.g., recruitment is faster than anticipated or a safety issue is identified.

17.7. Public and Patient Involvement

Patient and public involvement (PPI) has been involved in the design of the study which has included reviewing the patient facing documents and ensuring the delivery of the trial is achievable and manageable for participants. PPI representatives sit on the TSC and Co-applicants group to ensure the views of the public are always represented. Throughout the lifetime of the trial, the PPI team will be involved in reviewing amendments to the trial protocol and/or trial documents.

17.8. Research Team

Each site research team should have a minimum of two of the following roles named on the SSDL to oversee the Rabbit study: Surgeon, endocrinologist or radiologist.

Each site research team will have a medically qualified clinician to act as the Lead PI and they may be any of these roles above. The PI is responsible for the overall conduct of all study related activities at the site including compliance with the protocol.

In addition, there should also be a research nurse and a data manager or clinical trial administrator within the research team.

17.9. Finance

The research costs of the trial are funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) grant NIHR135261 awarded to Mr Neil Sharma, University of Birmingham. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess intervention costs associated with the trial, e.g., gaining consent, are estimated in the Schedule of Events Cost Attribution Tool. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

18. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments and relevant subsequent amendments which include the Data Protection Act 2018; and the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments). The protocol will be submitted to and approved by the REC prior to the start of the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

The Trial Office may be required to submit a progress report to UoB Research Governance Team (RGT) annually starting 12 months after the date of the favourable opinion was given. An electronic copy will be emailed to RGT within 30 days of the end of the reporting period.

19. DATA PROTECTION AND CONFIDENTIALITY

Personal data and sensitive personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments). Personal data categories that will be collected include: Name, date of birth, NHS number, e-mail address, postal address.

Participants will only be identified by their unique trial identification number on eCRFs and on any correspondence with the Trial Office. Participants will acknowledge the transfer and storage of their ICF to the Trial Office. This will be used to perform central monitoring of the consent process.

In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records. Representatives of the RABBIT trial team and sponsor may be required to have access to participants' notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. The Trial Office will maintain the confidentiality of all participant data and will not disclose information by which participants may be identified to any third party.

20. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

21. INSURANCE AND INDEMNITY

UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to UoB for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

22. POST-TRIAL CARE

At the end of the trial, participants will continue with standard of care with their usual clinical team.

23. ACCESS TO FINAL DATASET

The final dataset will be available to members of the Trial Management and co-applicant group who need access to the data to undertake the final analyses.

Requests for data generated in this trial will be considered by BCTU. Data will typically be available six months after the primary publication unless it is not possible to share the data (for example: the trial results are to be used as part of a regulatory submission, the release of the data is subject to the approval of a third party who withholds their consent, or BCTU is not the controller of the data).

Only scientifically sound proposals from appropriately qualified Research Groups will be considered for data sharing. The request will be reviewed by the BCTU Data Sharing Committee in discussion with the CI and, where appropriate (or in absence of the CI) any of the following: the Trial Sponsor, the relevant TMG, and/or the independent TSC.

A formal Data Sharing Agreement (DSA) may be required between respective organisations once release of the data is approved and before data can be released. Data will be fully de-identified (anonymised) unless the DSA covers transfer of participant identifiable information. Any data transfer will use a secure and encrypted method.

24. PUBLICATION PLAN

The protocol will be made available on the RABBIT Trial website (www.birmingham.ac.uk/Rabbit).

On completion of the trial, the data will be analysed, and a Final Study Report prepared.

Outputs from the trial will be submitted for publication in peer reviewed journals and the findings of the trial will be made public. Manuscripts will be prepared by the TMG and submitted for publication.

In all publications, authors should acknowledge that the trial was performed with the support of NIHR HTA and BCTU. Intellectual property rights will be addressed in the Clinical Study Site Agreement between the Sponsor and site. The results of the trial will be made available to participants in a plain English summary.

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