The Efficacy and Cost effectiveness of Real Time Ultrasound Elastography in The Investigation Of Thyroid Nodules and the diagnosis of thyroid cancer.

ElaTION

ElaTION TRIAL PROTOCOL

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FOR SAFETY REPORTING

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Sponsor: University of Birmingham.

Signatures

The investigators and the sponsor have discussed this protocol. The investigators agree to perform the investigation and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

Chief Investigator

Professor Hisham Mehanna

Signature and date: _____ _ _/_ _/_ _ _ _

Sponsor statement:

Where the University of Birmingham takes on the role of sponsor for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

Abbreviations

AE	Adverse event
AR	Adverse reaction
BCTU	Birmingham Clinical Trials Unit at the University of Birmingham
CI	Chief Investigator
DMEC	Data Monitoring and Ethics Committee
FNA	Fine Needle Aspiration
FNAC	Fine Needle Aspiration Cytology
GCP	Good Clinical Practice
HRA	Health Research Authority
HTA	Health Technology Assessment
InHANSE	Institute of Head and Neck Studies and Education
ISRCTN	International Standard Randomised Controlled Trial Number
PI	Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
RR	Relative Risk
RTE	Real Time Elastography (Strain or Shear Wave)
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
US-FNAC	Ultrasound - fine needle aspiration cytology

CONTENTS

ELATION TRIAL SUMMARY

Trial design: Pragmatic randomised controlled trial with 1:1 randomisation.

Objectives: The primary objective is to determine if real time elastography (RTE) in conjunction with fine needle aspiration cytology (FNAC) will reduce the number of patients who have a non-diagnostic **first** FNAC result as compared to conventional ultrasound (US) only guided FNAC.

Outcome measures

Primary outcome measure

The proportion of patients who have a non-diagnostic (Thy1) cytology result following the first FNAC.

Secondary Outcome measures

1. Number of FNACs required to obtain a definitive diagnosis[1];
2. Time from first FNAC to obtaining a definitive diagnosis;
3. The proportion of patients with benign histology results following thyroidectomy;
4. Proportion of patients who have thyroidectomy;
5. Accuracy of a cytology result for first FNAC and repeated FNAC in relation to overall definitive diagnosis;
6. Accuracy of an imaging assessment on ultrasound (with or without RTE) alone diagnostic protocol in relation to overall definitive diagnosis;
7. Patient reported outcome measures of depression and anxiety, pain, and quality of life: the Hospital Anxiety and Depression rating Scale (HADS), Visual Analogue Pain Score (VAPS) and EQ-5D quality of life score;
8. Radiologist report of whether RTE had contributed to the radiologist's decisions, how easy they found using RTE, and whether they found it helpful above using US-alone in predicting malignancy;
9. Complication rate from any thyroidectomy at 30-days and 6-months post-surgery – to include haematoma rate and temporary hypocalcaemia rate at 30 days and vocal cord palsy and permanent hypocalcaemia at 6 months post-operative;

[1] Definitive diagnosis is defined as: obtaining two benign (Thy 2) FNAC results; obtaining a single benign (Thy 2) result with a U2 benign ultrasound; obtaining histopathological diagnosis following a Thy 3, Thy 4, or Thy5 result; or obtaining histopathological diagnosis following persistently non-diagnostic (Thy 1) FNAC results

10. Resource usage for consultation time and diagnostic testing procedures and subsequent management including consultations and surgical treatments.

Eligibility criteria

Inclusion criteria

1. Patients with single or multiple thyroid nodules whether solid or partially cystic (ie: mixed), undergoing investigation who have not undergone previous thyroid FNAC within the last 6 months.
2. Aged 18 or over.
3. Patient able and willing to give written informed consent.

Exclusion Criteria

1. Patients who have undergone previous thyroid FNAC within the last 6 months.
2. Patients with a bleeding diathesis that precludes FNAC (not including patients currently on warfarin or aspirin therapy).
3. Patients with a needle phobia.
4. Pregnant patients.
5. Patients with purely cystic nodules or with recent haemorrhage, with no solid component.
6. Thyroid nodules that appear to have Rim or egg shell calcification.

Patient population and sample size: Patients aged 18 years old or over with a thyroid nodule or nodules, detected on palpation by the clinician (clinically palpable) or identified incidentally by imaging performed for non-thyroid pathology e.g. cervical spondylosis. The target sample size is 968 patients.

Trial duration: 5 years

Trial treatment / intervention:

Intervention arm- Strain or shear wave elastography (RTE)-guided FNAC. RTE is a technology that can be added at the same time as the routine ultrasound examination, and may help differentiate benign from malignant nodules based on the compression characteristics of the two, as well as identify the areas of malignancy within nodules.

Control arm- Routine US-only guided FNAC (the current standard recommended by the British Thyroid Association guidelines).

1. BACKGROUND

1.1. Thyroid Nodules

Palpable thyroid nodules can be detected in about 5-7% of the population[1]. Using ultrasound, nodularity of the thyroid can be detected in up to 50% of the population[2]. Approximately 4-7% of thyroid nodules are malignant, and hence most national guidelines recommend the investigation of nodules larger than 5mm-10mm in diameter[3;4]. Our meta-analysis of incidental thyroid nodules identified on imaging for non-thyroid conditions, also demonstrated a malignancy rate of 4.5% (Mehanna, unpublished data). Therefore, thyroid nodules identified incidentally on imaging appear to carry a similar risk of malignancy when compared with nodules that are clinically evident or palpable, and should therefore be investigated in the same way as palpable nodules.

Due to the increased use of imaging modalities, such as ultrasound carotid duplex and MRI for cervical spinal disease, incidental thyroid nodules that are asymptomatic are increasingly being detected and investigated. This is resulting in a rapidly increasing burden of investigation of thyroid nodules[5]. In one average-sized hospital, over a period of 5 years, 1412 ultrasound-guided fine needle aspirations were undertaken for the investigation of thyroid nodules - an average of 282 scans per year[6].

1.2. Current recommended classification and investigation of thyroid nodules

Definitive investigation of thyroid nodules is by ultrasound and fine needle aspiration cytology (FNAC) according to the 2014 British Thyroid Association (BTA) guidelines[3]. Ultrasound can detect features that predict the risk of malignancy with accuracy varying from 22-89%[7]. FNAC is performed by inserting a small-bore needle into the thyroid nodule, which is either done by palpation or under ultrasound-guidance. FNAC remains best practice for diagnosing thyroid malignancy.

The BTA 2014 guidelines[3] recommend a classification of the results of FNAC, with subsequent management based on this classification. The recommendations for this study, based on he guidelines, are as follows:

- Thy 1 – non diagnostic: BTA guidelines recommend repeat US guided FNAC, especially if there is suspicion of malignancy, up to 2 times, If Thy 1 is obtained in all three instances, our recommendation is to surgically remove nodules.
- Thy 2 – benign: guidelines recommend a further benign FNAC if there are suspicious features or indeterminate features on histology or ultrasound. Whilst discharge after a single benign FNA result can be considered if no suspicious features exist, we request a second US FNA to allow examination of the false negative rate of a single Thy2 policy.
- Thy3a denotes neoplasm possible, atypical features present but not enough to place into other categories. Usually a repeat US FNA is recommended. For repeated Thy3a, consider MDT discussion and consideration of surgery.
- Thy 3f denotes follicular neoplastic lesion of indeterminate cytology, which may be benign or malignant.
- Thy 4 is suspicious of cancer.
- Thy 5 is diagnostic of malignancy.

The BTA recommendation is to surgically remove nodules with repeated Thy 3f, 4 and 5 cytology results to obtain definitive histological diagnosis.

In a 2012 audit of 1412 consecutive US FNAs in one institution, 20% of the FNA results were Thy 1, 70% Thy 2, 5% Thy 3 (3a and 3f), 3% Thy 4 and 2% Thy 5 [6].

1.3. Current deficiencies in the investigation and diagnosis of thyroid nodules

1.3.1 Non-diagnostic and false-positive results

Whilst FNAC is the most reliable diagnostic technique, it is subject to sampling and analysis uncertainties, depending on several factors including identifying the correct nodule and the correct part of the nodule to perform the FNAC, as well as the deficiency of cytology to differentiate follicular carcinomas from adenomas.

FNAC carries a non-diagnostic rate of up to 20%[6;8]. The 2014 BTA guidelines recommend repetition of FNAC after obtaining non-diagnostic (Thy 1) samples if there is a suspicion of malignancy at least once, preferably under ultrasound-guidance. If 2-3 non-diagnostic results are obtained, and there is a suspicion of malignancy, a diagnostic hemi-thyroidectomy is usually recommended. Ability to reduce Thy1 rate and subsequent surgery would be highly beneficial.

Thy 3 nodules are also malignant in approximately 20% of cases, meaning that 80% will have a benign nodule, which did not need to be removed. The sampled nodule turns out to be malignant in about 80% of Thy 4 cases and 98-99% of Thy 5 cases.

Therefore, Thy 3, 4 and 5 results when considered together, there is a false positive rate (overall approximately 24%), defined as patients with benign disease (no cancer) having diagnostic operations which could have been avoided. It would be beneficial to improve this so that less thyroidectomy operations are done for benign nodules.

1.3.2 Diagnostic accuracy of ultrasound alone

Ultrasound alone has a variable diagnostic accuracy for predicting malignancy. In addition, there have been few large scale prospective studies on its accuracy as a sole diagnostic tool within a randomised multi-centre setting.
Ascertainment of its accuracy and that of the new elastography technique before widespread roll-out would be of benefit.

1.4. Importance of the ELaTION Trial

This study is important because of the following factors:

i. **A significant health need:**

Thyroid nodules affect a large proportion of the population, and are increasingly being identified incidentally on routine imaging of the head and neck. There is a need to improve the performance of US-FNAC and hence reduce the number of FNACs and diagnostic operations needed to establish a diagnosis. This may reduce the morbidity associated with the procedures (e.g. permanent loss of voice, difficulty swallowing, permanent hypocalcaemia requiring life-long medication), and decrease the inconvenience and anxiety shown to be associated with uncertainty before diagnosis, especially on repeated tests[9].

ii. **Considerable potential resource and cost requirements**:

Thyroid nodules are very common, affecting up to 50% of population and are increasingly being detected due to increasing use of imaging technology. This could result in a significant financial burden to the NHS[5].

Decreasing the number of non-diagnostic FNAC and of operations undertaken could result in considerable NHS savings.

iii. Outstanding issues in FNAC.

There remain some important questions regarding the use of ultrasound alone for diagnosis and the need for repetition of US-only guided FNAC, which have, to date, not been addressed in a large prospective randomised setting and lack level 1 evidence.

1.5. Shear and strain wave elastography (RTE)

Elastography is a recently developed technology that can be used as an adjunct to US-guided FNAC. RTE combines the diagnostic advantages of US-guided FNAC with an assessment of the lesion's stiffness to increase the accuracy of thyroid cancer diagnosis. Malignant thyroid nodules are harder than benign ones[(10)]. The comparative amount and pattern of soft to hard areas within the nodule indicates the likelihood of malignancy, and can help the operator choose the nodule with the highest risk of malignancy in order to biopsy it. Potentially, it can also help to direct the radiologist undertaking the needle biopsy to the areas that are most likely to be malignant within the nodule. Hence, potentially, RTE may also increase the yield of positive FNAC results[(11)]. A meta-analysis [(12)] of 638 patients from 11 studies showed that RTE features alone had a pooled sensitivity of 92% (CI 88-96) and specificity of 90% (CI 85-95) for identifying malignant thyroid nodules. Most studies have also shown very good correlation between radiologists[(13)].

There are two elastography methods currently available; strain elastography (also known as 'real-time elastography') and shear wave elastography.

Strain elastography requires physical pressure on the target lesion, usually provided by minimal pressure from the transducer, which allows for examination of the stiffness of the tissue, and displays this on the ultrasound screen as a colour coded map. The harder tissue e.g. a malignant thyroid nodule is a seen as a distinct area of colour (often coded red or blue) separate from normal background tissue. A strain ratio may be calculated from the differences in colour between the hard and soft tissue.

Shear wave elastography is generated by a pulse from the ultrasound transducer, and is a quantitate measurement of the velocity of sound in tissue; shear waves are faster in harder and therefore presumed malignant tissue. The various velocities measured can also be displayed in a colour map. Shear wave gives the same information about tissue hardness of the lesion, and more importantly can quantify the differences between normal and abnormal tissue

Both methods of elastography provide the same basic assessment of the underlying hardness of the tissue and may be used interchangeably to assess a focal thyroid lesion.

1.6. The need for ElaTION: a large, multi-centre, randomised controlled trial

In view of conflicting results from some of the retrospective and prospective case series and the fact that most results are single institution reports, a RCT is required to provide evidence of the role of RTE in the diagnosis of thyroid nodules. If proven effective in reducing the need for FNAC and also the false positive rates of FNAC it has the potential to reduce healthcare costs and patient distress significantly. In addition, ElaTION will attempt to answer some of the important outstanding questions in thyroid ultrasonography – mainly the efficacy of ultrasound-only protocols and the need for repetition of Thy2 US FNAC in the diagnosis of thyroid nodules.

2. TRIAL DESIGN

2.1. Design

ElaTION is a pragmatic, multi-centre randomised controlled diagnostic trial which will compare the use of elastography in conjunction with US–guided FNAC (the intervention) with conventional US-only guided FNAC (current practice).

2.2. Objectives

Primary objective:

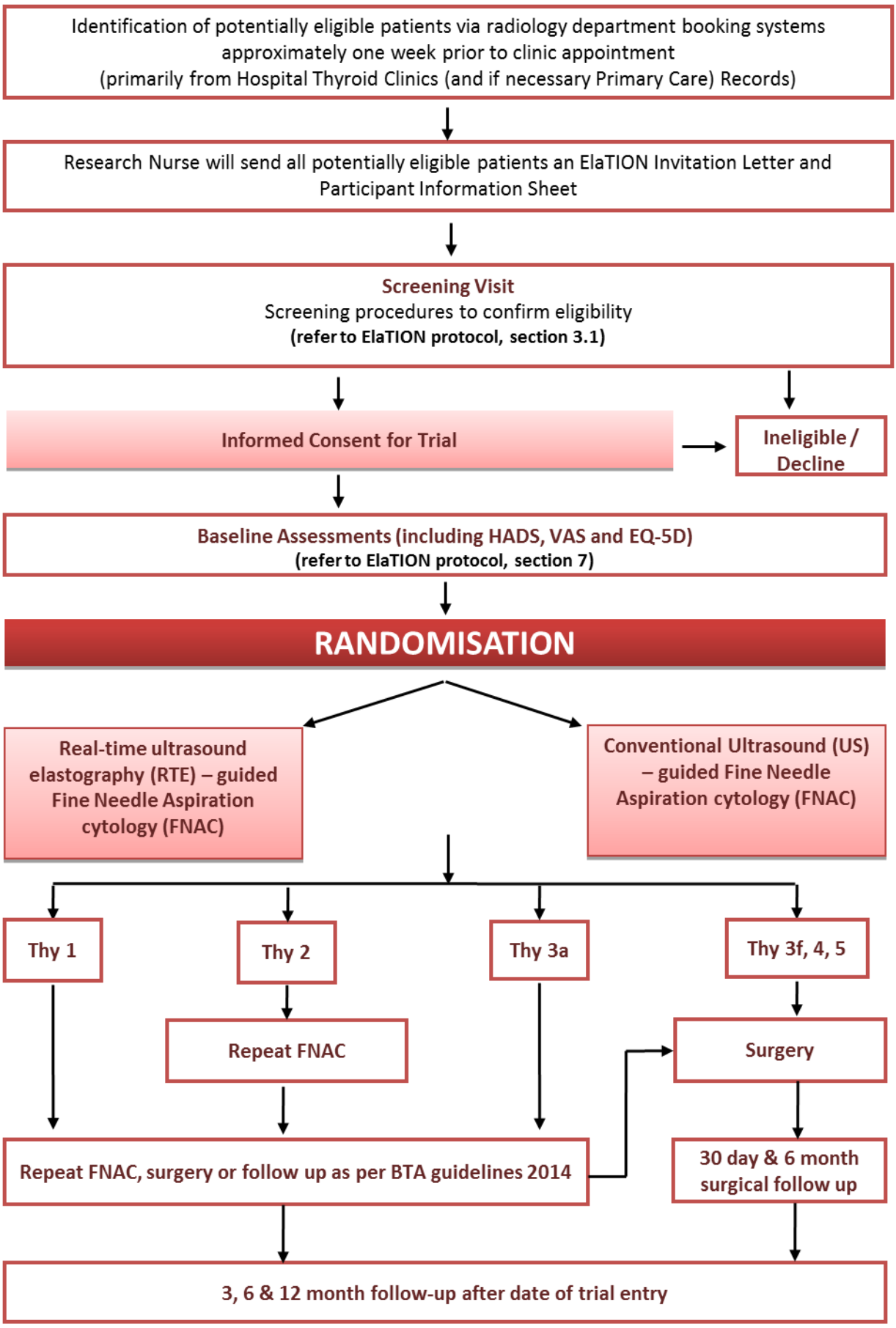
The primary objective is to determine if RTE in conjunction with ultrasound to guide FNAC will reduce the number of patients who have a non-diagnostic (Thy 1) FNAC result following the first FNAC assessment as compared to conventional ultrasound-only guided FNAC.

Secondary objectives:

The secondary objectives are to evaluate:

1. Whether RTE compared to US reduces the total number of FNACs required to reach a definitive diagnosis;
2. Whether RTE compared to US reduces the time from first FNAC assessment until definitive diagnosis;
3. Whether RTE compared to US reduces the false positive rate i.e. the number of patients who receive a benign histology following surgery;
4. Whether RTE compared to US reduces the non-diagnostic (Thy 1) rate following all FNAC;
5. WhetherRTE compared to US reduces the number of patients having thyroidectomy;
6. Whether ultrasound alone is an accurate diagnostic modality for malignant thyroid nodules;
7. Whether RTE and US without FNAC is as accurate as RTE or US with FNAC;
8. Whether patients' anxiety, quality of life and patient reported procedural pain are improved using RTE-FNAC compared to US-FNAC;
9. The value of RTE in radiologist decision making and undertaking of FNAC;
10. Complication rates of thyroidectomy;
11. Whether RTE-FNAC is cost effective compared to current practice of US-FNAC.

2.3. Trial Schema


Identification of potentially eligible patients via radiology department booking systems approximately one week prior to clinic appointment (primarily from Hospital Thyroid Clinics (and if necessary Primary Care) Records)
Research Nurse will send all potentially eligible patients an ElaTION Invitation Letter and Participant Information Sheet
Screening Visit
Screening procedures to confirm eligibility
(refer to ElaTION protocol, section 3.1)
Informed Consent for Trial
Ineligible / Decline
Baseline Assessments (including HADS, VAS and EQ-5D)
(refer to ElaTION protocol, section 7)
RANDOMISATION
Real-time ultrasound elastography (RTE) – guided Fine Needle Aspiration cytology (FNAC)
Conventional Ultrasound (US) – guided Fine Needle Aspiration cytology (FNAC)
Thy 1
Thy 2
Thy 3a
Thy 3f, 4, 5
Repeat FNAC
Surgery
Repeat FNAC, surgery or follow up as per BTA guidelines 2014
30 day & 6 month surgical follow up
3, 6 & 12 month follow-up after date of trial entry

3. ELIGIBILITY

3.1. Inclusion and Exclusion Criteria

In order that patients are randomised into the ElaTION trial, patients must fulfil all eligibility criteria. Investigators will be asked to confirm eligibility criteria at randomisation.

Inclusion criteria

1. Patients with single or multiple thyroid nodules, whether solid or partially cystic (ie: mixed), undergoing investigation who have not undergone previous FNAC in the last 6 months.
2. Aged 18 or over.
3. Patient able and willing to give written informed consent.

Exclusion criteria

1. Patients who have undergone previous thyroid FNAC within the last 6 months.
2. Patients with a bleeding diathesis that precludes FNAC (patients currently on warfarin and aspirin therapy are eligible).
3. Patients with a needle phobia.
4. Pregnant patients.
5. Patients with purely cystic nodules or with recent haemorrhage, with no solid component.
6. Thyroid nodules that appear to have Rim calcification or egg shell calcification

Patients with single or multiple cysts

The presence of a cyst or multiple cysts often precludes a RTE scan being done because the cyst may not have sufficient amounts of surrounding solid thyroid tissue. Patients with these nodules will be excluded from the study. However, to ensure that an accurate and representative picture of current practice is obtained and an accurate assessment of the exact usefulness of the technique in routine clinical practice, we will collect anonymised data about those patients, even though they will not be randomised.

3.2. Identifying potential participants for consent

It is anticipated that patients will be identified for inclusion in the ElaTION trial prior to attending a radiology session for US-FNAC of the thyroid.

Nurses or researchers at participating trusts will identify potentially eligible patients at their initial consultation or via review of the radiology department booking systems one week prior to their scheduled appointment.

Sites will be provided with an ethically approved patient invitation letter (Appendix A) which the nurse (or other member of the research team) can send to eligible patients to invite them to participate in the study. The Patient Information Sheet (PIS) (Appendix B) should also be sent with the invitation letter.

Patients will be asked to attend approximately 30 minutes prior to their scheduled appointment (exact length of time is as per local preference) in order to discuss the trial and be asked to consent.

The research nurse or the researcher may contact the eligible patients in order to check that they have received the PIS and invitation letter and that they are happy to arrive prior to their scheduled appointment.

To exclude patients with purely cystic nodules with no solid component, it will be necessary to perform an US. Therefore, patients who otherwise meet the eligibility criteria and who agree to

consent for entry into the study should be consented and the radiologist will perform a brief US to determine the presence or absence of such nodules, this will be prior to randomisation. Those patients found to have purely cystic nodules will then be excluded from the trial and will not receive a randomised allocation; details of these patients should be recorded on the ElaTION Screening Log.

3.2.1 Obtaining consent

The patient's written informed consent to participate in the trial must be obtained prior to performing any trial related procedure, prior to randomisation and after a full explanation of the study has been given. The PIS is provided to facilitate this process.

If the participant expresses an interest in participating in the trial, they will be asked to sign and date the latest version of the Consent Form (Appendix C). The participant must give explicit consent for the regulatory authorities, members of the research team and representatives of the sponsor to be given direct access to the participant's medical records. The investigator (or delegate) will then sign and date the form. Written informed consent will be obtained by a trained member of the research team (with GCP training, knowledge of the trial protocol, and delegated authority from the local PI).

Within the ElaTION trial, it is anticipated that consent will usually be obtained by an ElaTION research nurse at site. However, consent can also be obtained by the Consultant Radiologist or by a delegated person e.g registrar, radiographer or sonographer.

Once written informed consent is obtained, the original copy should be kept in the ElaTION study site file, one given to the patient, one kept in the patient's notes and one sent to the ElaTION study office.

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 the discussion, version number of the PIS given to the participant and version number of the consent form signed and date consent received.

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 will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial will remain.

Informed consent must be obtained before any trial-related procedures are undertaken. In ElaTION, as purely cystic nodules are an exclusion criterion, patients will need to undergo a brief US after consent, but prior to randomisation to determine eligibility (see 3.2).

A separate consent form will be signed by participants who are willing to give blood and tissue samples for the purpose of translational research.

3.2.2 Informing the participant's GP

The patient's GP should be notified, with the patient's consent, and a specimen "Letter to GP" is supplied (Appendix D).

3.3. Screening logs and acceptance rate

In order to ascertain generalisability, a log will be kept of all patients who were potentially eligible

and were approached to participate in the study, if they were randomised or not and the reason for non-randomisation.

4. RANDOMISATION

4.1. Randomisation method and stratification variables

Patients will be randomised into the ElaTION trial in a 1:1 ratio between RTE-guided FNAC and conventional US-guided FNAC.

A 'minimisation' procedure using a computer-based algorithm will be used to avoid chance imbalances in important stratification variables.

The stratification variables will be:

1. Radiologist: as ultrasound and RTE scans are operator dependent.

2. Solitary nodule versus multi-nodular: as multiple nodules can affect the utility and accuracy of RTE.

3. Size of nodule (≤4cm vs >4cm).

4. Solid versus mixed solid and cystic nodules. Completely cystic nodules or recent haemorrhage within a cystic nodule with no solid area are excluded: RTE and FNAC cannot be used in a completely cystic lesion.

A random factor will be incorporated into the randomisation to reduce predictability and thus avoid selection bias. This means that each patient will have a probability (unspecified here) of either being minimised, or of receiving the opposite intervention to the one they would have received if they had been minimised.

4.2. Randomisation

Once eligibility has been confirmed and after written informed consent has been obtained, patients can be randomised into the trial.

Patients are randomised into the trial online at the ElaTION website,
https://www.trials.bham.ac.uk/ElaTION
Or by telephone call to the randomisation service (0800 953 0274)

Telephone randomisation is available Monday-Friday 0900-1700.

Online randomisation is available 24 hours a day, 7 days a week apart from short periods of scheduled maintenance and occasional network problems.

For the secure online randomisation website, each randomiser will be provided with a unique username and password.

Information is needed on number of nodules and their nature (solid or mixed) to enable randomisation.

If multiple nodules are found, randomisation should use the nodule most suspicious at the time of US.

Randomisation forms (Appendix E) will be provided to investigators and should be used to collate the necessary information prior to randomisation. The person randomising will need to answer all of the questions before an allocation and a trial number is given.

5. TREATMENT ALLOCATIONS

5.1. Experimental Arm – Strain or shear wave RTE in conjunction with Ultrasound-guided Fine Needle Aspiration cytology

RTE is a technology that can be used at the same time as the routine ultrasound examination. RTE may help differentiate benign from malignant nodules based on the compression characteristics of the two (as benign nodules are less firm than malignant ones). It would also help identify the best part within the nodule to obtain an FNA. This may help reduce sampling errors and also improve the accuracy of the first FNA, by guiding the radiologist to the nodule that is most likely to be malignant. RTE may also help guide the radiologist to the parts of large heterogeneous nodules that are most likely to contain malignant cells. This may also improve the nodule diagnostic rate (i.e. reduce the non-diagnostic rate).

All repeat FNAC must be undertaken using the same ultrasound technique as the first one specified by the randomisation and ideally by the same RTE-accredited radiologist.

5.1.1 Training and accreditation for RTE

Radiologists and senior sonographers trained and accredited in RTE and US-FNAC of the thyroid will deliver the intervention.

As elastography is not yet commonly used in the UK, and many radiologists do not have experience of this technique, all participating radiologists and any senior sonographers delivering the intervention, will be required to attend a training and accreditation module developed for the ElaTION trial.

STEP 1: Participating radiologists will need to submit an audit of the FNAC results of 20 consecutive FNACs that they have undertaken in the last 18 months, and the total number of US FNACs undertaken in the last year.

STEP 2: Participating radiologists will attend a workshop on RTE.

STEP 3: Following the workshop, the radiologist will use RTE in conjunction with normal ultrasound on 15 patients in their normal radiology lists in their trusts to gain experience. A logbook of cases will be required with outcome of the FNAC result.

STEP 4: Do a 'hot case' accreditation – where the radiologist will perform RTE ultrasound on one patient attending a radiology list and indicate which nodule they would sample. Following successful completion of the programme, accreditation in RTE will be awarded.

STEP 5: The scans of the first 5 RTE cases done by each radiologist will be reviewed by the Trial Central Radiology Panel.

STEP 6: Online elastography community: as part of radiologist's ongoing training, complex cases can be circulated via email for further discussion by all the radiologists. The email address for circulation of cases is elation@lists.bham.ac.uk. Once the radiologists have completed the accreditation process they will be added onto the list by the ElaTION trial coordinator.

5.2. Control Arm – Conventional Ultrasound-guided Fine Needle Aspiration cytology

Conventional grey scale and colour Doppler US-guided FNAC for all the FNACs required until a definitive diagnosis is obtained.

All repeat FNAC must be undertaken using the same ultrasound technique as the first one specified by the randomisation and ideally by the same RTE-accredited radiologist.

5.3. Other management at discretion of local doctors

Apart from the trial treatments allocated at randomisation, all other aspects of patient management are at the discretion of the local doctors, with no other special treatments or investigations and no additional follow-up visits.

5.4. Withdrawal from randomised allocation or protocol violation

Patients may withdraw at any time during the trial if they choose not to continue, or if their clinical team feel that continued participation in the trial is inappropriate.

There are different types of withdrawal:

- The patient does not want to attend trial specific follow-up visits, but has agreed to be followed-up according to standard practice (i.e. has agreed that follow-up data can be collected at standard clinic visits)
- The patient is not willing to be followed up for trial purposes at any further visits (i.e. has agreed that any data collected prior to the withdrawal of consent can be used in the trial final analysis)

Full details of the reason(s) for withdrawal should be recorded on the Case Report Forms (CRFs) if healthcare professional-initiated, otherwise a simple statement reflecting patient preference will suffice. Patients who withdraw from trial treatment, but continue with on-going follow-up and data collection should be followed-up in accordance with the protocol.

5.5. Blood and tissue sample collection- ElaTION Collect (Translational research)

Blood samples – 20 ml EDTA and 20ml cf-DNA of blood sample, to be used in translational research, will be collected prior to the first FNAC if the patient has consented for this at trial entry. The blood sample should be labelled with the trial number and patient initials. If missed prior to the first FNAC, blood samples can still be collected up until the time of surgery; the blood sample tubes should be annotated with the date collected. The tube should be sealed and sent in the blood box provided to the ElaTION COLLECT laboratory at InHANSE. For those patients who undergo surgery, follow up bloods at 3 and 12 months post-surgery will also be requested, further bloods will be requested from the time of recurrence if during the 12 month follow up period.

FNAC samples and FFPE blocks – Provided the patient has not withheld consent for tissue to be donated and used for research, one slide from FNAC and tissue from the time of surgery (if surgery occurs), should be sent to the ElaTION COLLECT Sample Lab at InHANSE

For each patient undergoing surgery, two FFPE block of normal tissue and two FFPE blocks of tumour tissue should be sent. In addition, should a neck dissection be performed, two blocks of normal lymph node and, if applicable, two blocks of involved lymph nodes should be sent. These samples will be used for translational research.

Quality assurance samples – These are separate to the translational tissue collection samples. To ensure quality assurance, all Thy 3, 4 and 5 FNACs, a random sample of 5% of all Thy 1 & 2 FNACs and all thyroidectomy histological samples will undergo central review by the ElaTION cyto/histopathologists. These will be requested by the ElaTION Trial Office and are to be sent to the Central Review Team directly at The Pennine Acute Hospitals NHS Trust .

Full details for the preparation and sending of blood and tissue samples are provided in the appendices. For quality assurance of tissue samples please refer to page 15.

5.6. Compatibility with other studies

Patients can be in both ElaTION and other non-interventional trials.

A patient can be part of both ElaTION and another interventional trial, provided the other trial does not affect i) the decision to do a US-FNAC and ii) the decision to undertake surgery based on the FNAC result. Please contact the ElaTION trial office to discuss these patients' eligibility prior to entry into ElaTION or other studies.

6. SAFETY MONITORING PROCEDURES

The collection and reporting of data on adverse events and serious adverse events will be in accordance with ICH GCP and the Research Governance Framework 2005. It is imperative that all investigators have a thorough understanding of anticipated adverse events and the reporting process of these events.

There are no Investigational Medicinal Products (IMPs) used as part of this trial. As all of the surgical techniques being tested in this trial are used as standard practice there are no (serious) adverse events which would be anticipated as a unique consequence of participation in the trial. Any trial-related serious adverse events (SAEs) which require immediate reporting will be reported on a trial-specific SAE form and will follow the procedure and timeframes outlined in this section of the protocol.

Other outcomes, which may also be considered safety outcomes, but which are anticipated outcomes for this group of patients, will be captured on the routine follow-up CRFs (30-day and 6-month Post-Operative CRFs), these include:

- Vocal cord palsy
- Temporary or permanent hypocalcaemia
- Haematoma
- Infection
- Re-operation due to surgical complications

6.1. General Definitions

Adverse Events (AEs)

An AE is any untoward medical occurrence in a subject to whom a research treatment or procedure has been administered, including occurrences which are not necessarily caused by or related to that treatment or procedure.

Adverse Reactions (ARs)

An AR is any untoward and unintended response in a subject which is caused by or related to a research treatment or procedure**.**

Serious Adverse Events (SAEs)

An SAE is an untoward event which:

- Results in death
- Immediately threatens the life of participant*
- Results in hospitalisation or a longer than anticipated stay in hospital
- Results in a persistent or significant disability
- Results in any congenital anomaly or birth defect in any pregnancy

*Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Non-serious adverse events/reactions

Most AEs that occur in this trial, whether they are serious or not, will be 'expected'. Non-serious adverse events/reactions will be recorded in the medical records and routine follow-up CRFs.

Expected SAEs

The following are SAEs that could be reasonably expected for this group of patients during the course of the trial:

- Recognised side-effects of the treatment or disease, or an event which is secondary to those recognised effects.
- Hospitalisations for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Hospitalisations for treatment, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study, and did not worsen
- Admission to a hospital or other institution for general care, not associated with any deterioration in condition
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

For the purposes of this trial these expected SAEs do **NOT** require reporting on an SAE form. These events should continue to be recorded in the source data according to local practice and be included on the routine follow-up CRFs (the 30-Day Post-Operative Assessment CRF and the 6-Month Post-Operative Assessment CRF)

Disease related morbidity and routine treatment or monitoring of a pre-existing condition that has not worsened will **NOT** be considered as SAEs and should **NOT** be reported to the Trial Office.

6.2. Serious Adverse Events for expedited reporting

SAEs occurring within 1 week (and not listed as 'expected' as defined above) will always be reportable to the ELaTION Trial Office on an SAE form. The assessment of relatedness to the trial intervention is a clinical decision and will be based on all available information at the time.

SAEs outside of this timeframe can also be reported if it is the opinion of the Investigator that there is a possible causal relationship to another aspect of the trial. An assessment of relatedness and expectedness will also be undertaken by the Chief Investigator (or delegated deputy).

All SAEs will be followed-up until the event has resolved or a decision has been taken for no further follow-up.

6.3. Reporting SAEs

All SAEs must be recorded on the SAE Form and faxed to the ELaTION Trial Office on 0121 415 8871 within 24 hours of the research staff becoming aware of the event.

The Principal Investigator (or other nominated clinician) has to assign seriousness and causality to the SAE before reporting.

For each SAE, the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates; times, if applicable)
- action taken
- outcome
- causality, in the opinion of the investigator*

*Assessment of causality must be made by a doctor. If a doctor is unavailable, initial reports without causality assessment should be submitted to the BCTU by a healthcare professional within 24 hours, but must be followed up by medical assessment as soon as possible thereafter, ideally within the following 24 hours.

The local investigator and others responsible for patient care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors and provide further follow-up information as soon as available.

6.4. Notification of deaths

All deaths will be reported to the BCTU on the SAE Form (Appendix K) irrespective of whether the death is related to disease progression or an unrelated event. If a participant dies, any post-mortem findings must be provided to the BCTU with the SAE form. The BCTU will report all deaths to the DMEC for continuous safety review.

6.5. Pharmacovigilance responsibilities

Local Principal Investigator (or nominated individual in PI's absence):

- Medical judgement in assigning seriousness and causality to SAEs.
- To fax SAE forms to BCTU within 24 hours of becoming aware, and to provide further follow-up information as soon as available.
- To report SAEs to the trust if required, in line with local arrangements.
- To sign an Investigator's Agreement accepting these responsibilities.

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

- To assign causality and expected nature of SAEs.

- To review all events assessed as SAEs in the opinion of the local investigator.

Birmingham Clinical Trials Unit:

- To prepare annual safety reports to main REC and TSC.
- To prepare SAE safety reports for the DMEC at 12-monthly intervals.
- To report all fatal SAEs to the DMEC for continuous safety review

Trial Steering Committee (TSC):

- To provide independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies.
- To review data, patient compliance, completion rates, adverse events (during treatment and up to end of follow-up).
- To receive and consider any recommendations from the DMEC on protocol modifications.

Data Monitoring & Ethics Committee (DMEC):

- To review overall safety and morbidity data to identify safety issues which may not be apparent on an individual case basis
- To recommend to the TSC whether the trial should continue unchanged, continue with protocol modifications, or stop.

6.6. Notification of Serious Breaches of GCP and/or the protocol

A "serious breach" is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

The BCTU on behalf of the Sponsor shall notify the REC in writing of any serious breach of:

(a) the conditions and principles of GCP in connection with the trial; or

(b) the protocol relating to the trial, as amended from time to time, within 7 days of becoming aware of that breach.

The Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase.

7. FOLLOW-UP

Trial data will be recorded by hospital research staff on the paper Case Report Forms (CRFs) and submitted to the ElaTION Trial Office at the BCTU.

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the CRFs.

The ELaTION Delegation & Signature Log will identify all those personnel with responsibilities for data collection.

CRF versions may be amended by the ELaTION Trial Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the CRFs must be implemented by participating sites immediately on receipt.

7.1. Follow-up assessments

Follow-up will be undertaken for 1 year from randomisation or until definitive diagnosis has been obtained if not achieved during that first year. This will be sufficient time to allow for further FNACs if required after the first test. Also this allows sufficient time for any surgery to be undertaken and histological diagnosis to be available.

For both intervention and control arms, diagnosis and management will proceed as follows:

Thy1 - repeat FNAC, especially if suspicion of malignancy. If Thy1 on three FNACs, then the recommendation is made for diagnostic surgery.

Thy 2 - repeat FNAC within 3-6 months. If two benign (Thy2) FNAC results are obtained then patient can be discharged. Consideration for discharge with a U2 scan and one Thy2 is allowed, but is not recommended for the purposes of this study.

Thy 3a - repeat FNAC within 3-6 months or discussion with MDT. Surgery may then be advised

Thy3/3f/4/5 - surgery is necessary.

All repeat FNAC must be undertaken using the same ultrasound technique as the first one specified by the randomisation and ideally by the same RTE-accredited radiologist.

All follow-up data will be captured on the relevant CRF and returned to the ElaTION Trial Office.

7.2. Patient assessment

Patient reported assessments will be performed using commonly used, validated questionnaires:

1. EQ-5D questionnaire completed at: baseline (at recruitment); after surgery; and 3 , 6, and 12 months after randomisation.
2. Cost collection form for health resource usage, completed at baseline,3 , 6, and 12 months after first FNAC
3. Visual analogue pain score after every FNAC.
4. Hospital depression and anxiety score (HADS) questionnaire completed at: baseline; , 3, 6, and 12 months after randomisation.

Where possible, patient questionnaires should be completed when patients are attending hospital appointments. If this is not feasible, the questionnaires should be posted by a member of the research team at site, to the patient for completion at home.

7.3. Complication rates

Complication rates following thyroid operations will be recorded at 30 days and 6 months post-surgery.

Data will be collected on haematoma rate and temporary hypocalcaemia rate at 30 days and vocal cord palsy and permanent hypocalcaemia at 6 months post-surgery only.

7.4. Timing of assessments

Assessment Schedule	Prior to trial entry	Baseline prior to first FNAC	Immediately after any FNAC	After FNAC result	After surgery	30 days post-op	3 months post-randomisation	3 months post-op	6 months post-op	6 months post-randomisation	12 months post-op	12 months post-randomisation
Written Informed consent	X											
Review inclusion / exclusion criteria	X											
EQ-5D		X			X		X			X		X
Hospital Anxiety and Depression Scale (HADS)		X					X			X		X
Cost collection CRF					X		X			X		X
Blood sample collection		X						X			X	
Tissue sample collection*			X		X							
Histology Assessment CRF **					X							
Visual Analogue Pain Score			X									
FNAC Assessment CRF			X									
FNAC Result CRF***				X								
Surgical Decision Form				X								
Surgery and surgical complications CRF****						X			X			

* Cytology and Histology. Please refer to tissue collection guidelines on page 17.

**The accompanying histopathology report should also be sent with the completed histology assessment CRF.

***The accompanying radiology report should also be sent with the completed FNAC result form.

**** Completed using the 30-day Post-Operative Assessment CRF and 6-month Post-Operative Assessment CRF.

7.5. QUALITY ASSURANCE

Radiology

The first 5 US elastography scans of each radiologist will be reviewed by one of the Trial Radiology Panel (Professor Sidhu and Drs Richardson and Colley). Thereafter, a random sample of 10% of all scans will be reviewed by the Trial Radiology Panel. Discordances will be fed back to the relevant radiologists.

Cytology and histology

All Thy 3a, 3f, 4 & 5 FNACs and a random sample of 5% of all Thy 1 & Thy 2 FNACs and all thyroidectomy histological samples will be reviewed by one of the experienced thyroid cyto/histopathologists of the Trial's Reference Pathology laboratory.

7.6. Data handling and record keeping

7.6.1 Source data

Data should be collated directly from the patient (for Quality of Life and cost collection questionnaires) or from the patient hospital notes using the ELaTION case report forms. Within the ElaTION trial, source data is the participant's medical notes generated and maintained at site.

7.6.2 CRF completion

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

Data reported on each CRF should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the CRF. All missing and ambiguous data will be queried. All sections are to be completed.

7.6.3 Data management and validation

Data will be collected via paper CRFs: paper forms should be sent to the ELaTION Trial Office for central input. Data validation is built into the database, so that range, date and logic checks are performed at the point of data entry.

CRFs these must be completed, signed/dated and returned to the ELaTION Trial Office by the Investigator or an authorised member of the site research team (as delegated on the ELaTION Trial Signature & Delegation Log) as soon as possible. Entries on paper CRFs should be made in ballpoint pen, in black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Email and letter reminders will be sent to the investigator and research coordinator for missing CRFs; Data Clarification Forms (DCFs) will be sent to request missing data or to resolve data inconsistencies.

7.7. Definition of the End of Trial

The end of the trial will be 6 months after the last data capture, i.e. 6 months after the date of the last visit of the last patient undergoing protocol based treatment. Within ElaTION, the last visit is once the last participant has reached 1 year follow-up.

However, patients will be asked for permission to monitor long-term survival and recurrence rates through medical interventions, HES, ONS, cancer and other registry data and GP information.

The Trials Office will notify the REC the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.

A copy of the end of trial notification as well as the summary report is also sent to the University of Birmingham Research Governance Team at the time these are sent to the REC.

8. STATISTICAL CONSIDERATIONS

8.1. Outcome Measures

The reference standard for all FNAC assessments and results is the final definitive diagnosis.

Final definitive diagnosis is defined as:

- obtaining two benign (Thy 2) FNAC results;
- or obtaining one Thy2 FNAC with a U2 scan;
- or obtaining histopathological diagnosis following a Thy 3, Thy 3f, Thy 4, or Thy5 result;
- or obtaining histopathological diagnosis following persistently non-diagnostic (Thy 1) FNAC results.

8.1.1 Primary Outcome Measures

The primary outcome measure is the proportion of patients who have a non-diagnostic (Thy 1) FNAC result following first FNAC compared between the RTE-FNAC and US-only guided FNAC.

8.1.2 Secondary Outcome Measures

The secondary outcome measures for the study are:

1. Number of FNACs needed to obtain a definitive diagnosis in each patient;
2. Time from first FNAC to obtaining a definitive diagnosis in each arm;
3. The proportion of patients with a benign histology, compared between arms;
4. The proportion of patients who have a non-diagnostic (Thy 1) cytology result following any FNAC by arm;
5. The proportion of patients who receive surgery by arm;
6. Accuracy of 1st FNAC results and repeated FNAC results, compared between arms;
7. If RTE or US without FNAC is as accurate as RTE or US with FNAC, compared between arms;
8. Patient reported anxiety, pain and quality of life(by the HADS questionnaire, VAPS and EQ-5D) at baseline and at 3, 6 and 12 months post-randomisation;
9. Radiologist survey-completed by radiologists at the end of the procedure to identify whether radiologists found RTE had contributed to their decisions, ease of use, and their prediction of malignancy of the nodule using RTE or US features alone;
10. Complication rate from any thyroidectomy at 30-days and 6 months post-surgery - haematoma rate and temporary hypocalcaemia at 30 days and vocal cord palsy and permanent hypocalcaemia rate at 6 months.
11. Resource usage for consultation time and diagnostic testing procedures and subsequent management including consultations and surgical treatments.

8.2. Sample size

We plan to recruit a sample of 968 patients to achieve over 90% power for detecting the following difference in the primary outcome at the 5% significance level, allowing for 15% loss to follow-up.

An audit of US- only guided FNACs in one institution, suggested that Thy1s made up 20% of FNAC results [6]. This is likely to be an overestimate as this was including cystic nodules, so a more conservative estimate of 10% is assumed in calculating the sample size. The hypothesis is that using RTE in addition to US in guiding the FNAC would reduce the number of Thy1s to 4%. To detect this difference, with a continuity correction, requires 411 patients in each arm or 822 in total. Therefore, after adjusting for 15% drop-out rate, a total of 968 patients is required.

8.3. Projected accrual and attrition rates

Due to variations in their set-up time, centres will on average recruit for a period of 30 months. Each centre will on average recruit 2.5 patients per month during that period, or a total of approximately 30 per year. This is on average 25-30% of the total throughput of the participating centres.

8.4. Statistical Analysis

A separate Statistical Analysis Plan for the ElaTION trial provides a more detailed description of the planned statistical analyses. A brief outline of the planned analyses for the primary and secondary outcome measures which are part of the main trial is given below.

The primary comparison groups will be composed of those who are in the RTE-FNAC arm to those in the US-FNAC arm. Patients, not biopsies, will be the unit of analysis. All analyses will be based on the intention to test and treat principle, with all patients analysed in the arms to which they were allocated irrespective of compliance with the randomised allocated diagnosis tool, and all patients will be included in the analyses. For all tests, summary statistics will be presented and 95% confidence intervals will be constructed where appropriate. A p-value of <0.05 will be considered statistically significant, and there will be no adjustment for multiple comparisons.

8.4.1 Primary Outcome Analysis

The primary outcome analysis will be the proportion of patients in the RTE-FNAC arm who have a Thy1 result following their first FNAC compared with that in the US-FNAC arm.

The primary analysis will be using generalised linear mixed model where the minimisation variables will be included as fixed variables apart from radiologist which will be a included as a random effect. As a secondary analysis, a chi-squared or Fisher's exact test (as appropriate) will be used to compare the proportions of patients who have a Thy 1 first FNAC result between the arms. The denominator will be the number of patients randomised to each arm.

8.4.2 Secondary Outcome Analyses

The secondary outcome measures include a comparison of proportions between the RTE-FNAC and US-FNAC arms. These include:

- the non-diagnostic cytology (Thy 1) rate for any FNAC undertaken in each patient;
- the number of patients out of all randomised who have surgery but have a benign histology;
- the number of FNACs required to obtain a definitive diagnosis;
- the number of patients who had a benign (Thy 2) result following first FNAC and how this compares with subsequent FNAC results in accuracy;

- the number of patients who had a benign (U2) result on US scan and how this compares with subsequent FNAC results in accuracy
- and the complication rate following any thyroidectomy out of those who had surgery.

These will all be compared between the arms using a generalised linear mixed model and adjusting for the minimisation variables. A chi-squared or Fisher's exact text (as appropriate) will be performed as secondary analyses.

The number of overall FNACs required to reach a definitive diagnosis will be compared between the RTE and US arm using a chi-squared test for trend.

Time to diagnosis will be compared between arms using a log-rank test.

Sensitivities and specificities can be calculated following US-only and RTE-only guided protocols and US-guided FNAC and presented along with 95% confidence intervals using binomial exact methods. Comparisons will be made within each arm between the tests using McNemar's test.

Continuous measurements taken over time (e.g. HADS) will be analysed using .

A more detailed description of all analyses can be found in the ElaTION Statistical Analysis Plan.

8.4.3 Cost-effectiveness Analysis

If the use of elastography in conjunction with ultrasound to guide FNAC in subjects with a thyroid nodule or nodules is found to be an effective and improved approach to US-FNAC without RTE, then this has potentially important cost implications for the health care sector. For example, RTE may have the potential to increase the proportion of needle biopsies that are diagnostic, which may lead to potential savings for the health care provider, e.g. by avoiding the delay of essential treatment which may otherwise occur due to false-negative tests. However, this alternative approach may still incur additional costs depending on the staff time required and more costly diagnostic techniques being used. Therefore, all the associated resource use costs incurred by both diagnostic approaches considered in this analysis need to be assessed in conjunction with measures of effectiveness.

The cost data collection will be undertaken prospectively for the subjects in the study in order to inform the cost component of the cost-effectiveness analysis. The main resource uses monitored during the trial, which will be collected by the trial staff, will include the following:

1. Consultation time required to explain each diagnostic test for explanation and consent
2. Number of and type of diagnostic testing procedures implemented e.g. no. of FNACs
3. Resource uses involved in the diagnostic testing procedures
4. Resource use and staff time related to usual care

Unit costs will be obtained from standard sources and health care providers.

The aim of the economic evaluation is to determine the cost-effectiveness of implementing RTE in conjunction with ultrasound to guide FNAC in subjects with a thyroid nodule or nodules detected on clinical examination or identified incidentally by imaging performed for non-thyroid pathology. The cost-effectiveness analysis will take the form of a cost-utility analysis in which the outcome measure will be the cost per quality adjusted life year (QALY). This will be undertaken by utilising

the EQ-5D responses provided by the subjects over the 12 months of the study, and using these to detect changes in quality of life of patients over time.

The model-based analysis will be carried out following the conclusion of the data collection undertaken during the cohort study. A decision analytic model will be used which will incorporate both the cost and quality of life data collected during the course of the study. It is anticipated that the time horizon of the analysis will be one year, although this may be extrapolated beyond one year if realistic parameter values for this patient group can be obtained from the wider literature.

Analysis will be conducted from the NHS perspective. In particular, this analysis will focus on the cost and long-term impact on patients that initially received false-negative tests leading to essential treatment possibly being delayed, and importantly on patients who received diagnostic hemi-thyroidectomy after multiple non-diagnostic FNAC tests, when they may have not needed them if the diagnostic rate was higher by RTE FNAC.

The results of the economic analysis will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold value of acceptance by which the cost-effectiveness of the diagnostic strategies will be judged. Simple and probabilistic sensitivity analysis will be used to explore the robustness of these results to plausible variation in key assumptions and variations in the analytical methods used and to consider the broader issue of the generalisability of the results obtained from the economic evaluation.

8.5. Missing Data and Sensitivity Analyses

Appropriate sensitivity analysis will be employed to explore the potential bias and reduced statistical power associated with missing data.

8.6. Subgroup Analyses Variables

Subgroup analyses are planned on the stratification variables used for randomisation. These are: solitary nodule versus multi-nodular; the size of nodule (<4cm vs >4cm); and solid versus mixed solid and cystic nodules. Tests for interaction will be performed to assess whether the intervention effect differs between the strata. The study has not been powered to detect any differences in these subgroups so any significant results are purely hypothesis generating.

9. DATA ACCESS AND QUALITY ASSURANCE

9.1. Confidentiality of personal data

All data will be handled in accordance with the UK Data Protection Act 1998.

All CRFs will not bear the participant's name. The participant's initials, date of birth and trial identification number, will be used for identification.

Personal data and sensitive information required for the ElaTION Trial will be collected directly from trial participants and hospital notes. Participants will be informed about the transfer of this information to the ElaTION trial office at the BCTU and InHANSE and asked for their consent. The data will be entered onto a secure computer database, either directly via the internet using secure socket layer encryption technology or indirectly from paper by BCTU staff.

All personal information received in paper format for the trial will be held securely and treated as strictly confidential according to BCTU policies. All staff involved in the ElaTION Trial (clinical, academic, BCTU, InHANSE) share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be stored on a secure server at Birmingham Clinical Trials Unit (BCTU) under the provisions of the Data Protection Act and/or applicable laws and regulations.

9.2. In-house Data Quality Assurance

9.2.1 Monitoring and Audit

ElaTION will be centrally monitored; however, on-site monitoring may occur if triggered.
Investigators and their host Trusts will be required to permit trial-related monitoring and audits to take place by the ElaTION trial office, providing direct access to source data and documents as requested. Trusts may also be subject to inspection by the Research and Development Manager of their own Trust and should do everything requested by the Chief Investigator in order to prepare and contribute to any inspection or audit. Trial participants will be made aware of the possibility of external audit of data they provide in the participant information sheet.

9.3. Independent Trial Steering Committee

The TSC provides independent supervision for the trial, providing advice to the Chief and Co-Investigators and the Sponsor on all aspects of the trial and affording protection for patients by ensuring the trial is conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the Trial Office to the chairperson of the TSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

9.4. Data Monitoring and Ethics Committee

During the study, interim analyses of safety and outcome data will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with any other analyses that the committee may request. Further details of DMEC functioning are presented in the DMEC Charter.

9.5. Long-term storage of data

Archiving will be authorised by the BCTU on behalf of the Sponsor following submission of the end of trial report.

Principal Investigators are responsible for the secure archiving of essential trial documents (for their site) as per their NHS Trust policy. All essential documents will be archived for a minimum of 5 years after completion of trial.

Destruction of essential documents will require authorisation from the BCTU on behalf of the Sponsor.

10. ORGANISATION AND RESPONSIBILITIES

To ensure the smooth running of the trial and to minimise the overall procedural workload, it is proposed that each participating centre should designate individuals who would be chiefly responsible for local co-ordination of clinical and administrative aspects of the trial.

All investigators are responsible for ensuring that any research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, adverse reactions and other events or suspected misconduct through the appropriate systems.

10.1. Centre eligibility

Participating centres will be secondary care hospitals with radiology departments which undertake investigation of thyroid nodules and radiologists who have undergone training and accreditation for RTE.

10.2. Principal Investigator at each centre

Each Centre should nominate one person to act as the Local Principal Investigator. This person should be a consultant radiologist or head and neck or thyroid surgeon or endocrinologist.

The local PI shall bear responsibility for the conduct of research at their centre. The responsibilities of the local Principal Investigator will be to ensure that all medical and nursing staff involved in the care of patients are well informed about the study and trained in trial procedures, including obtaining informed consent. The local Principal Investigator should liaise with the ElaTION Trial Coordinator on logistic and administrative matters connected with the trial.

10.3. Research Co-ordinator at each centre

Each participating centre should also designate a researcher as local Research Coordinator; this is usually a research nurse. This person would be responsible for ensuring that all eligible patients are considered for the study, that patients are provided with study information sheets, and have an opportunity to discuss the study if required. The coordinator may be responsible for collecting the baseline patient data and for administering the follow-up evaluations. Again, this person would be sent updates and newsletters, and would be invited to training and progress meetings.

10.4. The ElaTION Trial Office

The ElaTION trial office will assist local PIs in obtaining Trust approval.

The ElaTION Trial Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing collaborating centres with the following trial materials:

- The Site File, containing all documentation required under ICH GCP to define the involvement of the centre in the trial as well as the participant information sheets, consent forms and trial schema.
- An online randomisation system, including individual log-ins and passwords and guidance.

Each of the above will be supplied to each collaborating centre, after relevant Trust approval has been obtained. Additional supplies of any printed material can be obtained on request. The Trial Office also provides the central randomisation service and is responsible for collection and checking of data (including reports of serious adverse events thought to be due to trial treatment), for reporting of serious adverse events to the sponsor and/ or regulatory authorities and for

analyses. The Trial Office will help resolve any local problems that may be encountered in trial participation.

11. RESEARCH GOVERNANCE

The trial will be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP), the UK Data Protection Act and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

All centres will be required to sign an Investigator's Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the TSC will decide whether any action needs to be taken, e.g. suspension of centre.

11.1. Regulatory and Ethical Approval

11.1.1 Ethical, Health Research Authority and Trust Management Approval

The Trial will obtain a favourable ethical opinion from a Research Ethics Committee (REC), determining that the trial design respects the rights, safety and wellbeing of the participants.

The ElaTION trial was brought under the Health Research Authority (HRA) approval process in August 2016. The HRA assesses governance and legal compliance and the ElaTION Trial Office is responsible for obtaining this approval.

The local Trust will conduct capacity and capability checks to assess the facilities and resources needed to run the trial, in order to give host site permission. The Trial Office is able to help the local Principal Investigator in the process of obtaining trust management approval by supplying the HRA Local Documents Package. The local Principal Investigator will be responsible for liaison with the Trust management with respect to locality issues.

Once Trust approval has been obtained, the ElaTION Trial Office will confirm that all appropriate site approvals are in place and that the radiology accreditation has been completed. When the ElaTION Trial Office, on behalf of the sponsor, has verified that all applicable regulatory requirements have been met, the Local PI will be informed that the study is open at the Trust and potential trial participants can then start to be approached. The Trial Office will send the Investigator's Site File containing all trial materials to the local Principal Investigator. .

11.2. Funding and Cost implications

The research costs of the trial are funded by a grant from the Health Technology Assessment programme of NIHR awarded to the University of Birmingham.

11.3. Sponsor

Sponsorship will be provided by the University of Birmingham upon signing of the Clinical Study Site Agreement with each trial site.

11.4. Indemnity

ElaTION was developed by the InHANSE team and the BCTU, and is funded by the Health Technology Assessment programme of NIHR.

The University of Birmingham is the trial 'sponsor.'

The Sponsor (University of Birmingham) holds Public Liability (negligent harm) and Clinical Trial (negligent harm) insurance policies, which apply to this trial. Participants may be able to claim compensation, if they can prove that the University of Birmingham has been negligent. However, as this clinical trial is being carried out in a hospital setting, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Compensation is only available via NHS indemnity in the event of clinical negligence being proven. University of Birmingham does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees.

Participants *may* also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University of Birmingham or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

There are no specific arrangements for compensation made in respect of any serious adverse events occurring though participation in the trial, whether from the side effects listed, or others yet unforeseen.

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

11.5. Clinical Trials Unit

Data from this trial will be handled by the BCTU and InHANSE at the University of Birmingham. BCTU is a full-time research facility dedicated to, and with substantial experience in, the design and conduct of randomised clinical trials. The BCTU recognises the responsibilities of a data management centre with respect to the ethical practice of research and the adequate protection of human subjects.

11.6. Confidentiality of Personal Data

The trial will collect personal data about participants, and medical records will be reviewed for all patients and routine physical examinations will be performed. Participants will be informed that their trial data and information will be securely stored at the trial office at the BCTU, and will be asked to consent to this. The BCTU and InHANSE abide by the UK law Data Protection Act 1998. The data will be stored on a secure computer database, and all personal information obtained for the study will be held securely and treated as strictly confidential. Any data processed outside of the BCTU and InHANSE will be anonymised.

11.7. Publication

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. Centres will be permitted to publish data obtained from participants in the ElaTION Trial that use trial outcome measures but do not relate to the trial randomised evaluation and hypothesis.

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