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

Version 2.0, 5th September 2014

Sponsor:	**University of Birmingham**
Chief Investigator:	**Professor Hisham Mehanna**
Coordinating Unit:	**Birmingham Clinical Trials Unit (BCTU) and Institute of Head and Neck Studies and Education (InHANSE)**
Funder:	**Health Technology Assessment**
ISRCTN:	**TBA**
Main REC Ref. No.:	**14/SC/1206**

Institute of Head and Neck Studies and Education

UNIVERSITY OF BIRMINGHAM

National Institute for Health Research

ElaTION Trial Management Committee

Chief Investigator

Professor Hisham Mehanna
Academic Thyroid Surgeon
University of Birmingham
Email: h.mehanna@bham.ac.uk

Trial Design and Statistics

Professor Jon Deeks
Professor of Biostatistics
University of Birmingham
Email: j.deeks@bham.ac.uk

Patient Representative

Judith Taylor
British Thyroid Foundation

Trial Management

Dr Laura Magill
Lecturer in Surgical Clinical Trials
University of Birmingham
Email: e.l.magill@bham.ac.uk

Ms Nicola Graham
InHanse Trials Team Lead
University of Birmingham
Email: n.graham@bham.ac.uk

Health Economics

Dr Andrew Sutton
Lecturer in Mathematical Modelling
University of Birmingham
Email: a.j.sutton@bham.ac.uk

Trial Steering Committee

(For independent oversight)

Chair: Professor James McCaul (Bradford Royal Infirmary)
Dr Susan Mallett (University of Oxford)
Mr James England (Hull Royal Infirmary)

Radiology

Dr David Richardson
Consultant Radiologist
Royal Victoria Infirmary, Newcastle
Email: david.richardson@nuth.nhs.uk

Dr Steve Colley
Consultant Radiologist
University Hospitals Birmingham
Email: steve.colley@uhb.nhs.uk

Dr Julie Olliff
Consultant Radiologist
University Hospitals Birmingham
Email: julie.olliff@uhb.nhs.uk

Endocrinology

Professor Jayne Franklyn
Professor of Endocrinology
University of Birmingham
Email: j.a.franklyn@bham.ac.uk

Dr Kristien Boelaert
Consultant Endocrinologist
University of Birmingham
Email: k.boelaert@bham.ac.uk

Cytohistopathology

Prof Tim Stephenson
Consultant Cytohistopathologist
Sheffield Teaching Hospitals
Email: tim.stephenson@sth.nhs.uk

Data Monitoring and Ethics Committee

(For interim analyses and response to specific concerns)

Chair: Dr Wai Lup Wong (Mount Vernon Cancer Centre)
Dr Laura Moss (Velindre Hospital)
Dr Gillian Lancaster (Lancaster University)

ElaTION Trials Office
University of Birmingham Clinical Trials Unit
College of Medical & Dental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT
Telephone: 0121 415 9105 (Voicemail outside office hours) Fax: 0121 415 8871

Email: ElaTION-trial@contacts.bham.ac.uk Website: www.birmingham.ac.uk/ElaTION
IT: Mr Nicholas Hilken Tel: 0121 415 9121 Email: n.h.hilken@bham.ac.uk

Clinical queries should be directed during office hours to an appropriate member of the Trial Management Group. Other queries should be directed to the ElaTION Trials Office.

FOR RANDOMISATIONS

TELEPHONE: 0800 953 0274 (UK) or +44 121 415 9137 (Outside UK)

FOR SAFETY REPORTING

Fax SAE Forms to 0121 415 8871

Version Number 2.0 5th September 2014

Previous Protocol Versions- Version 1.0 Dates 6th June 2014

ISRCTN

Funding Body

Health Technology Assessment (HTA)

Sponsor

University of Birmingham is the sponsor.

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

University of Birmingham Signature Date

Sponsor

Dr Sean Jennings

University of Birmingham Signature Date

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
HTA	Health Technology Assessment
InHANSE	Institute of Head and Neck Studies and Education
ISRCTN	International Standard Randomised Controlled Trial Number
MREC	Multicentre Research Ethics Committee
PI	Principal Investigator
PIS	Participant Information Sheet
RR	Relative Risk
RTE	Real Time Ultrasound Elastography
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

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

Objectives: The primary objective is to determine if RTE in conjunction with fine needle aspiration cytology will reduce the number of patients with benign thyroid nodules who have diagnostic thyroid operations as compared to conventional Ultrasound only guided FNAC.

Outcome measures:

Primary outcome measure

The rate of benign histology result following thyroid surgery, compared between the RTE-FNAC arm and the conventional US-FNAC arm.

Secondary Outcome measures

1. Overall number of FNACs required and time to obtain a definitive diagnosis in each arm.
2. Non-diagnostic cytology (Thy1) rate for the first FNAC undertaken in each patient.
3. Resource uses for consultation time and diagnostic testing procedures and quality of life (EQ-5D).
4. Predictive value of a benign (Thy2) cytology results for first FNAC and repeated FNAC in relation to overall definitive diagnosis for RTE-FNAC and conventional US-FNAC
5. Predictive value of a benign result on ultrasound alone and RTE-alone diagnostic protocols in relation to overall definitive diagnosis.
6. Patient reported anxiety (by Hospital Anxiety and Depression Score questionnaire) immediately before and after US FNAC, immediately before each consultation for results of US FNA or surgery and at 6 and 12 months from initial US-FNAC.
7. Radiologist survey-completed by radiologists at the end of the procedure to identify whether radiologists found US or RTE had contributed to their decisions, ease of use, and their prediction of malignancy of the nodule using RTE or US features alone.
8. Agreement rates for RTE between local operator and RTE core laboratory.
9. Patient reported pain (by visual analogue score) at procedure.
10. Complication rate from any thyroidectomy - haematoma rate, vocal cord palsy at 6 months, permanent hypocalcaemia rate at 6 months.

Eligibility criteria

Inclusion criteria

1. Patients with single or multiple thyroid nodules whether solid, cystic or mixed, undergoing investigation who have not undergone previous FNAC.
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
2. Patients with a bleeding diathesis that precludes FNAC.
3. Patients with a needle phobia.
4. Pregnant patients
5. Patients with purely cystic nodules or with recent haemorrhage, with no solid component

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.

Trial duration: 5 years

Trial treatment / intervention:

Intervention arm- Real-time ultrasound elastography – 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.

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

Sponsor: University of Birmingham

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 recent 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 US-FNAs scans 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 (US) and fine needle aspiration cytology (FNAC) according to the British Thyroid Association guidelines[3]. Ultrasound can detect features that predict the risk of malignancy with accuracy varying from 22-89%[7], but is not diagnostic. 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 British Thyroid Association (BTA) guidelines[3] recommend a classification of the results of FNAC, with subsequent management based on this classification. The classification is as follows:

- Thy 1 – non diagnostic: BTA guidelines recommend repeat US guided FNAC.
- Thy 2 – benign: guidelines recommend one further benign FNAC within a 6 month period before discharge. If a good sample was obtained, discharge after a single benign FNA result can be considered.
- Thy 3 denotes follicular neoplastic lesion of indeterminate cytology, which may be benign or malignant.
- Thy 4 is suspicious of cancer, and
- Thy 5 is diagnostic of malignancy.

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

In a recent audit of 1412 consecutive US FNAs in one institution, 20% of the FNA results were Thy 1, 70% Thy2, 5% Thy3, 3% Thy 4 and 2% Thy5 [6].

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

1.3.1 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.

Thy 3 nodules are 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 Non-diagnostic samples

FNAC also carries a non-diagnostic rate of up to 20%[6;8]. Guidelines recommend repetition of FNAC after obtaining non-diagnostic samples at least once, preferably under ultrasound-guidance. If 2-3 non-diagnostic results are obtained, a diagnostic hemi-thyroidectomy is usually recommended.

1.3.3 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 US alone for diagnosis and the need for repetition of US FNAC, which have to date, not been addressed in a large prospective randomised setting and lack level 1 evidence.

1.5. Real time ultrasound elastography (RTE)

Real time ultrasound elastography (RTE) is a recently developed technology that can be used as an

adjunct to Ultrasound-guided FNAC. RTE combines the diagnostic advantages of ultrasound-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].

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 false positive rates and the need for 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 trial (RCT) which will compare the use of Real Time Elastography (RTE) in conjunction with ultrasound to guide fine needle aspiration cytology FNAC (the intervention) with conventional ultrasound---only guided FNAC (current practice–comparator).

2.2. Objectives

Primary objective:

The primary objective is to determine if RTE in conjunction with fine needle aspiration cytology will reduce the number of patients with benign thyroid nodules who have diagnostic thyroid operations as compared to conventional ultrasound-only guided FNAC.

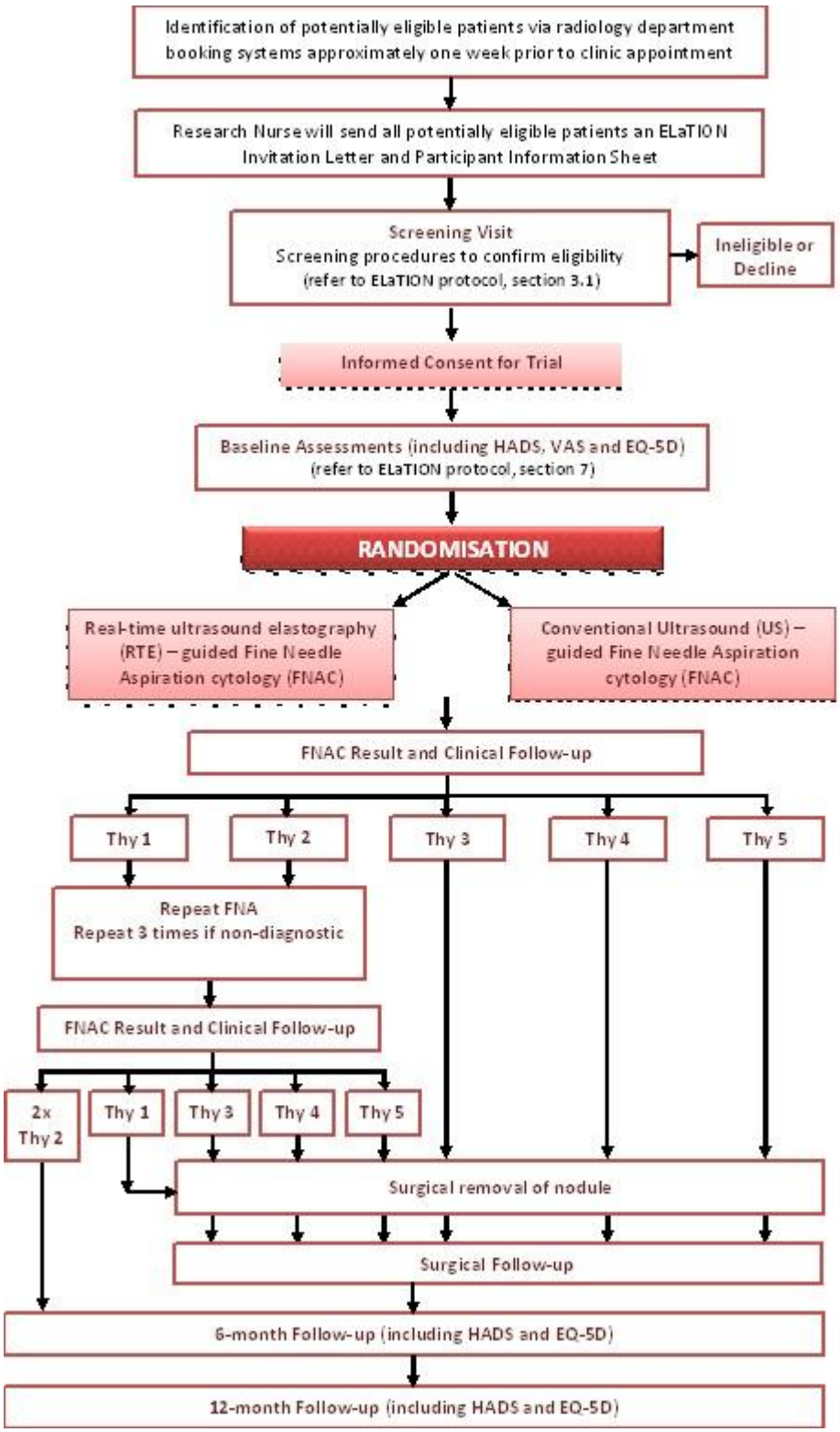
Secondary objectives:

The secondary objectives are to evaluate:

1. Whether RTE reduces the total number of FNAs and time required to reach a definitive diagnosis
2. Whether RTE reduces the non-diagnostic (thy1) rate
3. Whether RTE-FNAC is cost effective compared to current practice of US-FNAC
4. Whether repeated US FNAC and RTE FNAC following a benign first test improves diagnostic accuracy.
5. How the accuracy of ultrasound-only and RTE-only diagnostic protocols compare to the accuracy of US-FNAC and RTE-FNAC.

6. Whether patients' anxiety and quality of life improve because of quicker definitive diagnosis due to the new technology
7. The value of RTE as compared to US in radiologist decision making and undertaking of FNAC.
8. The accuracy of local operators compared to the RTE core laboratory
9. Procedure related pain reported by patients for RTE and US guided FNAC
10. Complication rates of thyroidectomy

2.3. Trial Schema



2.4. Outcome measures

Primary outcome measure

The primary outcome measure will be the rate of benign histology result following thyroid surgery, compared between the RTE-FNAC arm and the conventional US-FNAC arm. The rates are compared on the proportion within each arm.

Secondary outcome measures

The secondary outcome measures will be:

1. Overall number of FNACs required and time to obtain a definitive diagnosis in each arm.
2. Non-diagnostic cytology (Thy1) rate for the first FNAC undertaken in each patient.
3. Resource uses for consultation time and diagnostic testing procedures and quality of life (EQ-5D).
4. Predictive value of a benign (Thy2) cytology results for first FNAC and repeated FNAC in relation to overall definitive diagnosis for RTE-FNAC and conventional US-FNAC.(This will help model the feasibility of discharge after a Thy2 result after only one RTE-FNAC, compared to the current need for two Thy 2 results on US-FNAC).
5. Predictive value of a benign result on ultrasound alone and RTE-alone diagnostic protocols in relation to overall definitive diagnosis. (This will help model the accuracy of ultrasound only and RTE-only diagnostic protocols in identifying malignant nodules compared to US–FNAC).
6. Patient reported anxiety (by Hospital Anxiety and Depression Score questionnaire) immediately before and after US FNAC, immediately before each consultation for results of US FNA or surgery and at 6 and 12 months from initial US-FNAC.
7. Radiologist survey-completed by radiologists at the end of the procedure to identify whether radiologists found US or RTE had contributed to their decisions, ease of use, and their prediction of malignancy of the nodule using RTE or US features alone.
8. Agreement rates for RTE between local operator and RTE core laboratory.
9. Patient reported pain (by visual analogue score) at procedure.
10. Complication rate from any thyroidectomy - haematoma rate, vocal cord palsy at 6 months, permanent hypocalcaemia rate at 6 months.

Final "definitive" diagnosis is defined as obtaining two benign (thy2) FNA results, or obtaining a Thy3, 4 or 5 result or obtaining a histopathological diagnosis in persistently non-diagnostic (Thy1) results after repeated US-FNACs.

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, cystic or mixed, undergoing investigation who have not undergone previous FNAC.
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
2. Patients with a bleeding diathesis that precludes FNAC.
3. Patients with a needle phobia.
4. Pregnant patients
5. Patients with purely cystic nodules or with recent haemorrhage, with no solid component.

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 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.

The nurse will send eligible patients an invitation letter (Appendix A) to participate in the study plus the Patient Information Sheet (PIS) (Appendix B).

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.

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.

3.2.1 Obtaining consent

The patient's written informed consent to participate in the trial must be obtained before randomisation and after a full explanation of the study has been given. 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.

Once written informed consent is obtained (Appendix C), 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.

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).

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 present with single or multiple thyroid nodules, including those who are not randomised, their age and gender, the reason for non-randomisation, diagnostic procedure received and outcome.

4. RANDOMISATION

4.1. Randomisation method and stratification variables

Patients will be randomised into the ElaTION trial in a 1:1 ratio between Real-Time Elastography (RTE) used in conjunction with fine needle aspiration cytology and conventional ultrasound-guided fine needle aspiration cytology.

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 at unspecified periods during recruitment, the minimisation will be 'switched off', and patients will be simply randomised ignoring the stratification variables.

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 (completely cystic, solid or mixed) to enable randomisation. 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 – RTE in conjunction with Ultrasound-guided Fine Needle Aspiration cytology

Real-time ultrasound elastography (RTE)–guided Fine Needle Aspiration cytology (FNAC). 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). 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).

5.1.1 Training and accreditation for RTE

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

As Real Time Elastography (RTE) is not yet commonly used in the UK, and many radiologists do not have experience of this technique, all participating radiologists 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 and undertake a one day observership with a specialist radiologist experienced in thyroid RTE.

STEP 3: Following that, they will use RTE in conjunction with normal ultrasound on 25 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 they will each perform RTE ultrasound on one patient attending a radiology list and indicate which nodule they would sample. Following successful completion of the programme, they will be given an accreditation in RTE.

STEP 5: The scans of the first 10 cases done by each radiologist will be reviewed by the Trial Central Radiology Panel.

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

Conventional grey scale and colour Doppler ultrasound-guided FNAC for all the FNACs required to obtain a diagnosis for patients in the control arm.

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 would like to withdraw from the randomised allocation, but is willing to be followed-up according to the trial protocol (i.e. has agreed that follow-up data can be collected)
- 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

Blood samples – a 20 ml EDTA blood sample, to be used in translational research, will be collected prior to treatment if the patient has consented for this at trial entry. The blood sample should be labelled with the trial number and patient initials. The tube should be sealed and sent in the blood box provided to the ElaTION laboratory.

Tissue samples – Provided the patient has not withheld consent for tissue removed at FNAC and at surgery to be used for research will be sent to the ElaTION Trial Office. For each patient undergoing surgery, one FFPE block of normal tissue and two FFPE blocks of tumour tissue will be requested. These samples will be used for translational research.

All Thy 3, 4 and 5 FNACs, a random sample of 15% of all Thy 1 & 2 FNACs and all thyroidectomy histological samples will also be sent for review to the ElaTION cyto/histopathologists, via the ElaTION Trial Office.

Full details for the preparation and sending of blood and tissue samples are provided in the appendices.

5.6. Compatibility with other studies

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

If the patient is part of another interventional trial, they can still be recruited to ElaTION provided the other trial does not affect i) the decision to do an 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 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/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 case report forms (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:

- 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.

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 and expectedness 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, causality and expectedness 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*
- whether the event would be considered expected or unexpected*

*Assessment of causality and expectedness must be made by a doctor. If a doctor is unavailable, initial reports without causality and expectedness 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. If a participant dies, any post-mortem findings must be provided to the BCTU. The BCTU will report all deaths to the DMEC for continuous safety review.

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, expectedness 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 local committees 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 where it has not been possible to obtain local assessment
- 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 MREC 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

It will be the responsibility of the investigator to ensure the accuracy of all data entered in the case report forms (CRFs).

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

CRFs can be entered online at **http://www.trials.bham.ac.uk/ELaTION.** Authorised staff at sites will require an individual secure login username and password to access this online data entry system. If data is being collected on paper 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) within the timeframe listed below. 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.

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.

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.

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 recruitment. 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 per the British Thyroid Association Guidelines. This is as follows:

Thy1 - repeat FNAC. If Thy1 on three FNACs, then a 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.

Thy3/4/5 - surgery is necessary.

All repeat FNAC must be undertaken using the same ultrasound technique as the first one specified by the randomisation.

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 and patient diary for health economics analysis, completed at base line (at recruitment), 3, 6, and 12 months after first FNAC.
2. Visual analogue pain score after every FNAC.
3. Hospital depression and anxiety score (HADS) questionnaire - baseline (at recruitment), 3, 6, and 12 months after first FNAC.

Where possible, patient questionnaires should be completed when patients are attending for 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 immediately post-surgery and at 6 months surgery.

Data will be collected on haematoma rate and vocal cord palsy and permanent hypocalcaemia rate at 6 months.

7.4. QUALITY ASSURANCE

Radiology

The first 10 US elastography scans of each radiologist will be reviewed by the Trial Radiology Panel (Drs Richardson, Colley and Olliff). 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 3,4 & 5 FNACs and a random sample of 15% 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. Any cases showing discordance with the local centre result will be reviewed by the full panel. Discordances will be fed back to the relevant pathologists.

7.4.1 Timing of assessments

Assessment Schedule	Prior to randomisation	Baseline prior to FNAC	Immediately after any FNAC	Within 24 hours/ before any consultation for FNAC results	Within 24 hours/ before any consultation for surgery results	After surgery	6 months after first FNAC result	12 months after first FNAC result
Written Informed consent	X							
Review inclusion / exclusion criteria	X							
EQ-5D		X					X	X
Hospital depression and Anxiety Score (HADS)		X		X	X		X	X
Blood sample collection		X						
Tissue sample collection			X			X		
Visual Analogue Pain Score			X					
Clinical Follow-up Form			X					
FNAC Result				X				
Surgery and surgical complications Form					X		X	
Adverse event evaluation			X	X	X		X	X

7.5. Data management and validation

Data should be collated directly from the patient or the patient hospital notes using the ELaTION case report forms. Data should be entered as soon as possible onto the ELaTION database as soon as possible after collection by the Research Coordinator, investigator or local PI, who will be allocated personal usernames and passwords that restrict access to only participants at their centre. Alternatively, paper forms can 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. Email and letter reminders will be sent to the investigator and research coordinator for missing CRFs, missing data or data inconsistencies.

7.5.1 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.

7.6. Definition of the End of Trial

The end of the trial for regulatory purposes is defined as the date of the last visit of the last patient undergoing protocol based treatment. Within ElaTION, this is once the last participant has reached 1 year follow-up.

Long-term follow-up, to at least one year post-trial entry will constitute the end of the non-interventional phase of the trial. 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.

8. STATISTICAL CONSIDERATIONS

8.1. Outcome Measures

8.1.1 Primary Outcome Measures

The primary outcome measure is the rate of benign histology result following thyroid surgery, compared between the RTE-FNAC arm and the conventional US-FNAC arm.

8.1.2 Secondary Outcome Measures

The secondary outcome measures for the study are:

1. Non-diagnostic cytology (Thy1) rate for the first FNAC undertaken in each patient.

2. False negative rate of a benign (Thy2) cytology result on first FNAC in relation to overall definitive diagnosis, compared between RTE-FNAC arm and conventional US-FNAC arms.

Final "definitive" diagnosis is defined as obtaining two benign (thy2) FNA results, or obtaining a Thy3, 4 or 5 result or obtaining a histopathological diagnosis in persistently non-diagnostic (Thy1) results after repeated US-FNACs.

3. False negative rate of a benign result on ultrasound alone diagnostic protocols compared with US and FNAC in relation to overall definitive diagnosis, compared between RTE-FNAC arm and conventional US-FNAC arms.

Final "definitive" diagnosis is defined as obtaining one benign (thy2) FNA result, or obtaining a Thy3, 4 or 5 result or obtaining a histopathological diagnosis in persistently non-diagnostic (Thy1) results after repeated US-FNACs. Overall number of FNACs required to obtain a definitive diagnosis in each arm.

4. Cost-effectiveness analysis using EQ-5D.

5. A cost consequence analysis and a base case cost analysis will be performed. If these demonstrate cost-effectiveness, a model based analysis for longer-term effects may be undertaken. This is detailed in Section 9.3.3

6. Patient reported anxiety (by Hospital Anxiety and Depression Score questionnaire) immediately before and after US FNAC, immediately before each consultation for results of US FNA or surgery and at 6 and 12 months from initial US-FNAC.

7. 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.

8. Time from first FNAC to obtaining a definitive diagnosis in each arm.

9. Inter-operator correlation for RTE between local operator and RTE core laboratory.

10. Patient reported pain (by visual analogue score) at procedure.

11. Complication rate from any thyroidectomy - haematoma rate, vocal cord palsy at 6 months, permanent hypocalcaemia rate at 6 months.

8.2. Sample size

We plan to recruit a sample of 1000 patients to achieve over 90% power for detecting the following differences in the primary outcome at the 5% significance level, allowing for 15% loss to follow-up.

Persistent Thy 1, or any Thy 3 (follicular indeterminate), Thy 4 (pre-cancerous) and Thy 5 (cancerous) findings require surgery, following which definitive histology results are available. Benign findings on histology indicate that the surgery was unnecessary, and occurs in around 24% in current practice. The study is powered to detect a reduction to 15% with RTE-FNAC.

In addition, the study is powered at over 90% to detect a difference in the second outcome related to non-diagnostic findings. FNAC results are graded on a scale from Thy 1-Thy 5. Thy 1 indicates that results are non-diagnostic and require repeating. Audit of practice and research suggest a Thy 1 rate of up to 20% with US-FNAC, and we have powered the study to detect a reduction to 10% with RTE-FNAC.

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 receive a benign histology following thyroid surgery compared with that in the US-FNAC arm. A chi-squared or Fisher's exact test (as appropriate) will be used to compare the proportions of benign histology 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 the **first** FNAC undertaken in each patient; the number of patients who were classed as having a benign result following **first** FNAC but the definitive diagnosis was a Thy 3, Thy 4 or Thy 5 result; the number of overall FNACs required to reach a definitive diagnosis; the number of false negatives based on the radiologists prediction of malignancy following use of RTE or US features alone; the number of patients who had a false negative result following first FNAC in the RTE-FNAC arm compared with the number of patients who had a false negative result following second FNAC in the US-FNAC arm; and the complication rate following any thyroidectomy. These will all be compared between the arms using a chi-squared or Fisher's exact text (as appropriate). In the event that any important co-variables are unbalanced then a logistic regression model will be used adjusting for these variables.

Time to diagnosis will be compared between arms using a log-rank test and in the event of important co-variables being unbalanced, a Cox's proportional hazards model will be used adjusting for these variables.

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 can be made within each arm between the tests using McNemar's test.

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

8.4.3 Cost-effectiveness Analysis

If the use of Real Time Elastography (RTE) in conjunction with ultrasound to guide fine needle aspiration cytology (US-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. 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

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

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 according to the MRC Guidelines for Good Clinical Practice in Clinical Trials.

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 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 study office will assist local PIs in obtaining relevant Trust approvals.

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.
- An Investigators folder containing printed materials, such as participant information sheets, consent forms and trial schema
- An online randomisation system, including individual log-ins and passwords and guidance.

All 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. withdrawal of funding, suspension of centre.

The Trial Office will ensure researchers not employed by an NHS organisation hold an NHS honorary contract for that organisation.

11.1. Regulatory and Ethical Approval

11.1.1 Ethical and Trust Management Approval

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

The Local Comprehensive Research Network will conduct governance checks and 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 the site specific assessment by completing much of Site Specific Information section of the standard IRAS form as possible. The local Principal Investigator will be responsible for liaison with the Trust management with respect to locality issues and obtaining the necessary signatures at their Trust.

As soon as Trust approval has been obtained, the Trial Office will send a folder containing all trial materials to the local Principal Investigator. Potential trial participants can then start to be approached.

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 Institute of Head and Neck Studies (InHANSE) 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.

REFERENCE LIST

(1) **Deandrea M, Mormile A, Veglio M, Motta M, Pellerito R, Gallone G, et al. Fine needle aspiration biopsy of the thyroid: comparison between throid palpation and ultrasonography. Endocr Pract 2002;8:282-6.**

(2) **Hegedüs L. Clinical Practice. The Thyroid nodule. N Engl J Med 2004;351(18):1864-71.**

(3) **British Thyroid Association. Guidelines on the management of Thyroid Cancer. http://www.british-thyroid-association.org/Guidelines/ [Second]. 2007. 15-1-2014.**
Ref Type: Online Source

(4) **Cooper D, Doherty G, Haugen B, Kloos R, Lee S, Mandel S, et al. Revised American Thyroid Assiciation management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19(11):1167-214.**

(5) **Colley S, Olliff J, Shimal A, Page A. Rapid responses: radiological and cytological burden. BMJ 2009;338:b733.**

(6) **Al Maqbali T, Tedla M, Dekker A, Weickert MO, Mehanna H. Malignancy Risk Analysis in patients with inadequate fine needle aspiration cytology (FNAC) of the thyroid. PLoS One 2012;7(11).**

(7) **Bastin S, Bolland MJ, Croxson MS. Role of ultrasound in the assessment of nodular thyroid disease. J Med Imaging Radiat Oncol 2009;53(2):187.**

(8) **Cesur M, Corapcioglu D, Bulut S, Gursoy A, Yilmaz AE, Erdogan N, et al. Comparison of palpation-guided fine-needle aspiration biopsy to ultrasound-guided fine-needle aspiration biopsy in the evaluation of thyroid nodules. Thyroid 2006;16(6):555-61.**

(9) **Lang EV, Berbaum KS, Lutgendorf SK. Large-core breast biopsy: abnormal salivary cortisol profiles associated with uncertainty of diagnosis. Radiology 2009;250(3):631-7.**

(10) **Lyshchik A, Higashi T, Asato R, Tanaka S, Ito J, Mai JJ, et al. Thyroid gland tumor diagnosis at US elastography. Radiology 2005;237(1):202-11.**

(11) **Rago T, Scutari M, Santini F, Loiacono V, Piaggi P, Di Coscio G, et al. Real-time elastosonography: useful tool for refining the presurgical diagnosis in thyroid nodules with indeterminate or nondiagnostic cytology. J Clin Endocrinol Metab 2010;95(12):5274-80.**

(12) **Bojunga J, Herrman E, Meyer G, Weber S, Zeuzem S, Freidrich-Rust M. Real-time elastography for the differentiation of benign and malignant thyroid nodules: a meta-analysis. Thyroid 2010;20(10):1145-50.**

(13) **Kim JK, Baek JH, Lee JH, Kim JL, Ha EJ, Kim W, et al. Ultrasound elastography for thyroid nodules: a reliable study? Ultrasound Med Biol 2012;38(9):1508-13.**