The Rabbit Trial: Radiofrequency Ablation of Benign Intrathyroidal Tumours

The Rabbit Trial
Participant Information Sheet V5.0

Summary of the research

- Thyroid nodules are a very common cause of a lump in the neck.
- Most nodules are confirmed to be benign by tests including an ultrasound scan and a fine needle aspiration cytology (FNAC), also known as a needle biopsy test. These nodules can be left alone if they are not causing any troublesome symptoms.
- A few of these benign nodules grow to a size that can cause local symptoms such as pressure or pain or they can become unsightly to an individual.
- If treatment is required, the standard option is surgery with removal of either part of or the whole thyroid gland but this treatment may not be suitable for all patients.
- The introduction of radiofrequency ablation (RFA) has opened up a less invasive treatment option for these symptomatic nodules.
- This clinical trial will directly compare RFA to surgery as a treatment for thyroid nodules. It will help us find out whether RFA is as effective as surgery for symptom reduction, and if it is associated with fewer complications and improved cost effectiveness. Importantly, it will also enable us to establish if it is a more acceptable treatment for patients.

This Information Sheet

You are invited to take part in our research study. Joining the Rabbit Trial is voluntary. This Participant Information Sheet explains the purpose of the study, what will happen to you if you take part, and sets out detailed information about the way the study will be carried out. A member

of our research team will go through this information sheet with you, to help you decide whether or not you would like to take part and to answer any questions you may have. Please feel free to talk to others about the study if you wish. You can also contact the researchers, whose details can be found on the final page of this information sheet.
If you would like to take part we will give you information about why the research is being done and what this would involve for you. This is described in **Section 1**.
If you are interested in taking part after reading Section 1, please continue to **Section 2** which describes who is organising this study and how we will use the information we collect about you during the study.

Section 1

1. Purpose and background to the research

Historically, the treatment for compressive nodules was thyroid surgery but more recently the introduction of percutaneous thermal ablative techniques has opened up less invasive approaches. RFA has been approved by the National Institute for Health and Care Excellence (NICE) to treat benign thyroid nodules and further research into its clinical and cost-effectiveness has been recommended in NICE Guidelines. Few randomised controlled trials have examined the effectiveness of RFA compared to standard surgery for symptom reduction, complications, cost effectiveness and overall acceptability.

This trial is taking place all across the UK and will follow participants over 3 years from the start of the treatment. It will involve approximately 448 patients like you. Initially, we will be carrying out a feasibility of the study to see if we are able to recruit sufficient numbers of participants, and if so, the study will continue into a full trial. If we are unable to recruit the intended target, we may close the study earlier than planned.

2. Why have I been chosen?

We are inviting you to take part in this study because you have single or multiple thyroid nodules that are causing compressive or cosmetic symptoms and which affect your quality of life.
You have been identified by your ENT/surgical/endocrine team at your local hospital as someone who may be suitable to take part in this trial.

Before you decide whether or not you wish to take part, you should read the information below carefully and discuss it with your family, friends, endocrine, surgical or nursing team if you wish. Please take time to ask questions about the study, do not feel rushed or under any obligation to make a quick decision. It is important that you understand the risks and benefits of participating in this study so that you decide what is right for you. If you decide not to take part, your medical care will not be affected.

3. What would taking part involve?

When you have read this information sheet and asked any questions you have, if you then decide to take part in the study, we will ask you to sign a consent form. You will receive a copy of the signed consent form to keep. A member of the research team at your hospital will then arrange your initial screening appointment. The screening period is to confirm your eligibility and it may take place over a few appointments. The research team will ask you some questions about your medical history and carry out some physical assessments, such as vocal cord assessment, and specific blood tests if you haven't had these recently, to make sure you are well enough to participate in the trial and that your thyroid function and blood clotting are within the normal range. You may not be able to enter the trial if you are taking any of the following medications:

- Antithyroid drugs
- Thyroid hormone replacement
- Formal anticoagulation that cannot be paused for the intervention
- Clopidogrel that is not able to be stopped for a minimum of 5 days prior to the intervention
- Aspirin more than 75 mg once daily.

You may need to have a pregnancy test, this will be decided by your clinician. You may also need to have up to two needle biopsy tests to confirm that your nodule is benign and that you are eligible to enter the trial. You will also be asked if you are happy to receive participant questionnaires electronically or if you would prefer them to be sent to you by post with a pre-paid envelope to return to the RABBIT Trial Office once completed.

The questionnaires you will need to complete are as follows:

- ThyPRO – a multiple choice questionnaire that asks about your thyroid health and associated quality of life
- EQ-5D-5L – a multiple choice quality of life questionnaire asking you to rate your general health
- Pain VAS – the pain visual analogue scale, asking you to plot your pain score on a line
- Health Resource Usage Questionnaire (HRUQ) - asking about which health resources you have used and the impact of your health on your work.

You will be asked to complete the participant questionnaires at various timepoints during the trial as detailed in the table below. The approximate time it may take to complete questionnaires is also shown below.

Questionnaire	Screening appointment	After your procedure	3 months post-procedure	12 months post-procedure	24 months post-procedure	36 months post-procedure
ThyPro	✓		✓	✓	✓	✓
EQ-5D-5L	✓		✓	✓	✓	✓
Pain VAS	✓	✓	✓	✓	✓	✓
HRUQ			✓	✓	✓	✓
Approx time to complete	8-12 minutes	1 minute	10-15 minutes	10-15 minutes	10-15 minutes	10-15 minutes

Once your eligibility has been confirmed by a researcher and your questionnaires have been completed, your information will be entered into a secure online database, and a computer will then allocate one of the two groups for you at random:

- Hemithyroidectomy

OR

- Radiofrequency ablation

The researcher will let you know which group you have been put into. As it is a randomised trial, the process will ensure that there is an equal chance of your being placed in each of the groups. This is the best way to make sure there is a fair comparison between the different groups.

You will be booked in for your allocated procedure within 6 months of the randomisation date. On the day of the procedure, you will have some baseline assessments to make sure you are well enough to have the allocated procedure. You will need to have a pregnancy test even if you had one at screening. If this gives a positive result, you will not be able to have the procedure.

Hemithyroidectomy

You will be given an information leaflet on the operation by the team at your hospital. In summary, on the day of the surgery, you will be admitted to the ward and seen by one of the surgical and anaesthetic team. You will then be taken to theatre and have a general anaesthetic. Usually, you will have a cannula (small needle) inserted into the back of your hand for the anaesthetic to be delivered and may have an oxygen mask placed over your mouth and nose. The anaesthetist will let you know when you are about to fall asleep.

The surgery will involve an incision across the lower part of your neck. Your surgeon will try to make this incision in a natural skin crease to help minimize the scar. Important structures near your thyroid (such as the recurrent laryngeal nerve) will be carefully identified and protected before your thyroid is removed. The wound will be closed using sutures, these may be absorbable or non-absorbable. The procedure usually takes between 45 minutes and 2 hours. You will probably need to stay overnight in the hospital so you will need to bring an overnight bag.

Radiofrequency ablation
On the day of the procedure you will be seen by the team carrying out the ablation. They will talk you through the procedure and ask you to complete a consent form, and a pre procedural checklist. You will then be asked to change into a hospital gown.

Before the procedure starts, you will lie down on a bed with your neck extended. You may need to remove your trousers so that sticky pads may be placed on your thighs in order for the device to safely deliver the energy for your treatment into your thyroid. The person performing the procedure will scan your thyroid to plan the treatment.

The procedure will be performed under local anaesthetic injection to numb the area. This will stop any pain but you may feel the sensation of touch and pressure. A treatment needle will then be inserted through the skin (sometimes with a small incision across), and guided by ultrasound. Multiple ablations (heat treatments) will then be performed by moving the needle through the thyroid nodule. An electric current will be used to heat the needle tip, which destroys a small area of thyroid tissue. By moving the needle through the nodule, the whole nodule is eventually treated in order to shrink the gland.

The whole procedure will take approximately about one hour, or possibly longer depending on the size of your nodule. Once completed, the needle will be removed, and a dressing will be placed over the needle insertion site. A cold bag will be put on your neck to remove the heat.

After your treatment you will be in a recovery area to ensure your pain is manageable, you are not feeling sick and are able to eat and drink. You are likely to be discharged on the same day as the procedure, but a small number of people may need to stay longer or overnight.

Follow up
After your procedure you will have follow up appointments in clinic at 3 months, 12 months and 36 months. You will be asked to complete and return questionnaires at 24 months but you will not have a clinic visit for this. At the end of the trial, you will continue with standard of care with your usual clinical team.

4. When and how will I complete the questionnaires and tests?

At the screening visit, you will be asked whether you would prefer to receive your questionnaires electronically by e-mail or in paper format by post. If you opt to receive the questionnaires by post, we ask that you complete them and return them to the Rabbit Trial Office at the Birmingham Clinical Trials Unit (BCTU) in the pre-paid envelope supplied. The questionnaires must be completed and returned to the BCTU before you can be randomised.

The schedule of assessments and questionnaires is in the below table:

When	Where	Questionnaires	Assessments
Screening	Hospital	EQ-5D-5L ThyPRO Pain VAS	Medical history, vital signs, ultrasound guided needle biopsy test (this may be done at a separate visit, if needed) pregnancy test (if needed). Thyroid function blood test, blood clotting (INR) test and vocal cord mobility assessment if you have not recently had these
Randomisation visit	Hospital		Eligibility check and final confirmation, randomisation
Day of intervention	Hospital		Medical history, vital signs, height, weight, pregnancy test (if needed), allocated intervention procedure
Post-intervention or day of discharge	Hospital	Pain VAS	
3 months after intervention	Hospital	EQ-5D-5L ThyPRO Health resource usage Pain VAS	Thyroid function blood test, vocal cord mobility assessment, ultrasound (if on RFA arm), weight, physical exam (of neck)
12 months after intervention	Hospital	EQ-5D-5L ThyPRO Health resource usage Pain VAS	Thyroid function blood test, vocal cord mobility assessment (if vocal cord palsy at 3 months visit), ultrasound (if on RFA arm), weight, physical exam (of neck)
24 months after intervention	Remote	EQ-5D-5L ThyPRO	

		Health resource usage Pain VAS	
36 months after intervention	Hospital	EQ-5D-5L ThyPRO Health resource usage Pain VAS	Thyroid function blood test, ultrasound (if on RFA arm), weight, physical exam (of neck)

If you need assistance with completing the questionnaires please contact a member of the research team. If requested, we will post you a set of questionnaires with a prepaid envelope for you to return to the BCTU. Please return your completed questionnaires as promptly as possible. If we have not received your completed questionnaires after a reminder, a research team member may contact you. You may also be contacted if we have a query on your returned questionnaires (e.g. missing data) that requires clarification.

5. What are the possible benefits of taking part?

We cannot predict whether taking part in this study will be directly beneficial to you. However, the agreed benefits of the two procedures are outlined here.

Benefits of RFA

- Evidence shows RFA to be safe and effective in shrinking benign thyroid nodules which are causing symptoms, without the need for 'open' surgery or hospital admission. Taking part will confirm that this is the case.
- RFA is less invasive than surgery so there is less chance of developing an underactive thyroid gland in the long term. Therefore, thyroid hormone replacement is rarely needed after RFA.
- The incidence of vocal cord weakness is substantially lower with RFA than surgery.
- The incidence of most complications is lower with RFA compared to surgery.
- The recovery time is usually shorter than following surgery.
- RFA is done through a small incision and avoids a surgical scar.
- RFA is performed as a day case rather than an overnight admission.
- RFA can reduce the nodule volume by 35-60% at one month following treatment and 60-90% at 6-12 months depending on the size and consistency of the thyroid nodule.

Benefits of surgery

- A well-established procedure with a very high likelihood of cure.
- Extremely low chance of needing repeat surgery.

6. What are the possible disadvantages and risks of taking part?

All treatments and procedures have risks and the research team will discuss the risks of the procedures during the consent process.

Possible disadvantages and risks of RFA

Problems that may occur straight away

- Bleeding at the site of needle insertion and minor burning of the skin. This normally does not require any further treatment.
- Hoarseness of voice (occurring in 1-2 people in 100), which normally resolves a few hours after the procedure.

Problems that may happen later

- Rarely patients develop breakdown of the skin or a delayed burn a few days after the procedure (within 7 days). Most of these resolve without treatment but very rarely skin burns require dressing and treatment.
- There is a small risk (less than 1 person in 100) of infection following this treatment. We will advise you to look out for worsening pain, redness or swelling, which may require antibiotic treatment.
- It is possible that some nodules regrow years after RFA but there is not enough evidence to know how often this happens.

Problems that are rare, but serious.

- There have been reports of nodule rupture following the procedure, presenting as a sudden neck bulging and pain, and permanent damage of the nerve to the voice box, leading to voice changes (less than 2 people in 1000).
- Unlike surgery, larger nodules could require more than one treatment to effectively reduce nodule size.

Possible disadvantages and risks of surgery

- Haematoma, 1 in 10 risk close to trachea (wind pipe)
- Recurrent laryngeal nerve palsy (weakness) which can lead to a breathy voice. This risk is temporary in 1 in 20 patients and permanent in less than 1 in 100 patients. A nerve monitoring electrode will be used throughout your surgery to help minimize this risk
- Neck scarring
- Infection

If you do experience any complications, please contact your local site immediately (details are provided at the end of this information sheet).

Section 2

7. Who is organising and funding the research?

The Rabbit Trial is a national study run by the BCTU which is part of the University of Birmingham (UoB). The study is sponsored by the UoB, which has certain legal and ethical responsibilities for

the study (ref: RG_21-192). UoB has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial whereas the conduct of the trial at Site and other clinical care of the patient remains with the NHS organisation responsible for the Clinical Site. The UoB is the data controller for the personal data that we process in relation to you. The trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (ref: NIHR135261).

8. How have patients and the public been involved in this study?

When designing this study, we have consulted dedicated patient and public involvement (PPI) representatives on both our Trial Steering Committee and Co-applicants group. Our PPI representatives have helped to ensure that taking part in the trial will not take up too much of your time, and all of the information provided to potential participants is clear and comprehensive. This information sheet has been produced by researchers and PPI representatives working in partnership. In addition, members of the public sit on the Research Ethics Committee (REC) and they have reviewed this trial positively and given a favourable opinion (REC Ref.: 24/NW/0299). PPI input will continue to be an integral part of the trial.

9. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people (REC), to protect your interests. This study has been reviewed positively and given favourable opinion by the North West – Preston REC.

10. Will my taking part in this study be kept confidential?

How will we use information about you?

We will need to use information from you and from your medical records for this study. We need to process your information to conduct this research, which is a task performed in the public interest and for scientific or historical research purposes, statistical purposes or archiving purposes in the public interest. This information will include your name, date of birth, contact details, medical history and information collected at the clinic visits and through the questionnaires.

The only people allowed to look at the information will be the researchers who are running the study, authorised staff at UoB and your hospital, sponsor representatives, and the regulatory authorities who check that the study is being carried out correctly. In addition, information collected about you may be used to support other related research in the future, and may be shared anonymously with other researchers.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will ensure that we will collect and process only the minimal amount of personal data throughout the duration of the trial.

We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

If you would like the trial results to be sent to you, we will use your contact details to send a lay summary to you when the trial has ended.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information in the following ways:

- at www.hra.nhs.uk/information-about-patients/
- in our leaflet www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by emailing dataprotection@contacts.bham.ac.uk

11.What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak to a member of the research team who will do their best to answer your questions. Their contact details can be found at the end of this information sheet.

If you wish to complain formally, the usual NHS complaints procedures are available to you. Copies of these guidelines are available on request. If you wish to complain about how you have been treated during this study, please contact the Patient Advice and Liaison Service (PALS) at your local hospital. Contact details can be found on the end of this participant information sheet or on this website: https://www.nhs.uk/common-health-questions/nhs-services-and-treatments/what-is-pals-patient-advice-and-liaison-service/

If any undue harm is caused by participating in the trial which is related to the negligence of the University of Birmingham or its staff in the design or management of the trial, insurance is in place to ensure participants will be compensated for any such instances.

12. What if I do not want to take part?

Taking part in this study is entirely voluntary and the standard of care you receive will not be affected if you decide not to take part or would like to withdraw at any stage of the study.

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

If you decide to stop taking part during the study, we would like to continue collecting information about your health from your hospital. If you do not want this to happen, tell us and we will stop. Data collected up to the time of your withdrawal (or if you lose capacity to consent during the study) will be kept and used anonymously as part of the study outcome.
If you choose to withdraw from any aspect of participation, please speak to a research team member. Their contact details can be found at the end of this information sheet.

13. Will my expenses be reimbursed?

There is no travel or parking reimbursement available for our participants beyond that normally offered by the hospital.

14.What happens if new information becomes available?

Sometimes we get new information about the treatment being studied. If this happens, a member of the research team will tell you and discuss whether you should continue in the study. If your research doctor is happy for you to continue in the study, you will have the option to decide whether you wish to continue. A member of the research team may ask you to re-sign a consent form if you decide to continue.

If you decide not to carry on, a member of the research team will make arrangements for your standard clinical care to continue.

If however, a member of the research team considers that you should withdraw from the study, they will explain the reasons and arrange for your standard clinical care to continue.

15. What happens when the research study stops?

Your final follow up appointment in this study will be 36 months after the intervention. At the end of the study your local consultant will continue to look after you and your treatment, or you may be discharged to your GP.

16. What will happen to the results of the research study?

The findings of this study will be made public. We would like to publish our results in medical journals and present the findings at conferences, to help other doctors and medical staff learn from the findings and for patients to benefit. If we are successful with this, it will be in an anonymous manner so you cannot be identified. We also plan to inform all participants of the findings, highlighting where the results are expected to make a clinical difference on the Rabbit trial website and social media channels. This process will include both written material and a video. One of our PPI partners is the British Thyroid Foundation, and they will also report the results of the trial on their website (www.btf-thyroid.org), newsletter and social media channels. If you would like to be

informed of the trial results, we can send you a summary when the trial has ended using your contact details.

17. How will my personal data be kept secure?

The UoB takes great care to ensure that personal data is handled, stored and disposed of confidentially and securely. Our staff receive regular data protection training, and the University has put in place organisational and technical measures so that personal data is processed in accordance with the data protection principles set out in data protection law.
Any physical paperwork containing identifiable data will be kept in an access-controlled and secured room inside a locked filing cabinet.
In relation to this project, electronic data will be kept on secure, encrypted IT servers within the UoB.

18. How long will my personal data be kept?

Your data will be retained for 10 years after the publication of the research outcomes. If you withdraw from the study, we will keep the information we have already obtained and it will be anonymised before we include it in the final analysis.

Do you have any further questions?

Contact Information: If you would like to speak to someone about the study please contact:

Site to populate: *<PI name>< Job Title>*
<telephone and/or e-mail address>
For independent advice or support, you can also contact the NHS Patient Advisory and Liaison Service (PALS);
Tel: *<insert local PALS contact number(s)>* Email: *<insert local PALS email address>*

Rabbit Trial Office at the Birmingham Clinical Trials Unit
Email: RABBIT@bham.trials.ac.uk
Website: www.birmingham.ac.uk/Rabbit

Thank you for taking the time to read this information sheet and for considering taking part in this study.