IoN

IoN– **I**s ablative radi**o**iodine **N**ecessary for low risk differentiated thyroid cancer patients

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

We would like to acknowledge the members of the National Cancer Research Network (NCRN) head and neck patient consumer group who contributed to the set-up of this trial.

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1. Protocol Summary

1.1. Summary of Trial Design

Title:	IoN – **I**s ablative radi**o**iodine **N**ecessary for low risk differentiated thyroid cancer patients
Short Title/acronym:	IoN
EUDRACT no:	2011-000144-21
Sponsor name & reference:	University College London (UCL/10/0299)
Funder name & reference:	Cancer Research UK
ISRCTN no:	ISRCTN80416929
Design:	Multicentre randomised phase II/III trial
Overall aim:	Phase II: to examine feasibility of recruitment. Phase III: to determine whether disease-free survival among patients who do not have routine Radioactive iodine (RAI) ablation is non-inferior to those who do.
Primary endpoint:	Phase II: monthly patient accrual rates Phase III: disease-free thyroid-specific survival based on: 1) histologically confirmed structural loco-regional recurrent or residual disease 2) distant recurrence 3) death from thyroid cancer
Secondary endpoints:	Phase III: Cause Specific mortality Disease-free survival (using thyroid cancer recurrence/metastatic disease or death from any cause) Loco-regional recurrence Distant and biochemical recurrence Interventions for recurrence Additional investigations for recurrence Quality of Life Adverse events Incidence of second primary tumours Cost effectiveness
Target accrual:	560 patients (minimum of 450)
Inclusion & exclusion criteria:	Refer to sections 6.3 (Thyroid surgery) and 6.4 (Recommended surgery) for guidance and definition around surgery and inclusion into IoN

	TNM eligibility assessed against TNM7 (7th edition 2009).
	TNM8 (8th edition 2017, in use in the UK from 01/01/2018) is allowed and if used the following guidance should be used for **T3 and N categories which have changed from TNM 7 but the other categories of TNM remain unchanged for DTC.**
	Eligible (TNM8):
	• pT3a
	  ○ >4cm and confined to thyroid for PTC
	  ○ Only up to 4cm for FTC
	• PN1a level VI involvement
	Excluded (TNM8):
	• pT3b (any size with gross extrathyroidal extension involving strap muscles)
	• pN1a with level VII involvement
	
	Inclusion
	• Histological confirmation of well differentiated thyroid carcinoma: MDT decision for inclusion based on overall clinico-pathological assessment is critical.
	• R0 total thyroidectomy (in one or two stages, no residual disease present; Rx at the discretion of the MDT) within the last 6 months
	• Negative pregnancy test in women of child bearing potential
	• Aged 16 or over
	• WHO performance status 0 – 2, self-caring
	• Histological confirmation of differentiated thyroid carcinoma:
	MDT decision for inclusion based on overall clinico-pathological assessment
	• Papillary thyroid cancer
	  ○ Non aggressive histological features (small foci of aggressive histology allowed at the discretion of the MDT)
	  ○ pT1a (≤1cm) unifocal with positive level VI lymph nodes (pN1a)
	  ○ pT1a(m): all individual foci ≤1cm
	  ○ pT1b and pT1b(m): >1-2cm
	  ○ pT2 and pT2(m): >2-4cm
	  ○ pT3 and pT3(m): (TNM7) or pT3a and pT3a(m) (TNM8): >4cm confined to thyroid
	  ○ pT3 (TNM7) or pT1a/1b/2/3 (TNM8 where minimal microscopic extrathryoidal extension (ETE) does not change the T score) +/- (m): any size with minimal ETE if recommended by the MDT
	  ○ pN0

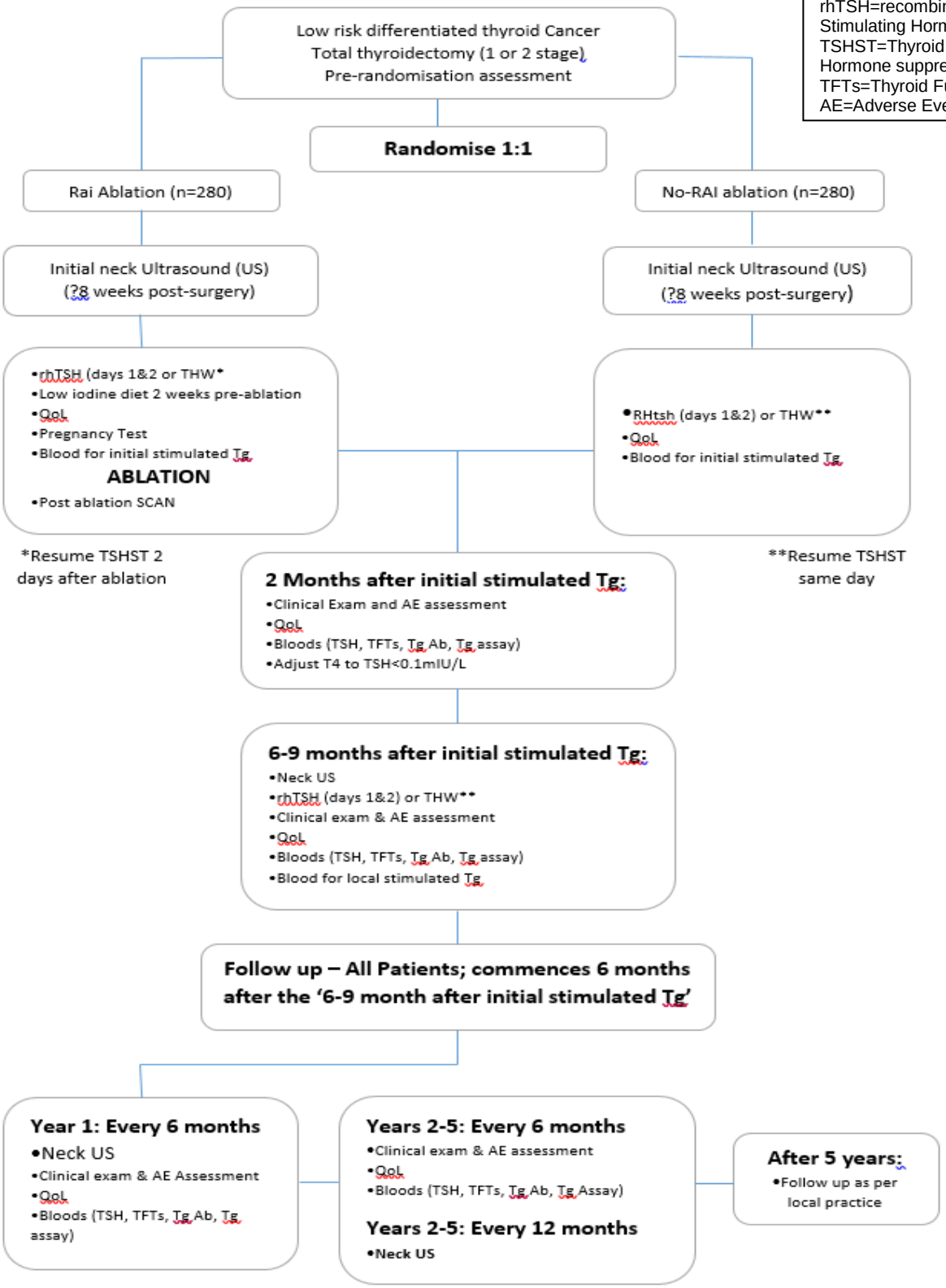
	○ pN1a ○ pNX • Encapsulated Follicular Variant of Papillary Thyroid Cancer (eFVPTC) with capsular invasion only. • Follicular thyroid cancer (FTC) (including oncocytic or HÜrthle cell cancer): ○ minimally invasive FTC – which are considered low risk and are recommended by the specialist MDT based on overall clinico-pathological assessment ▪ pT1b and pT2: >1-4cm intrathyroidal ▪ pT3 (TNM7) or pT1a/1b/2 (TNM8 where minimal microscopic ETE does not change the T score): any size up to 4cm with minimal ETE if recommended by the MDT. • Histological material available for Central Review • Willing to use contraception for the duration of the trial until 6 months post radioiodine treatment (for females) or 4 months post treatment (for males), if allocated to the ablation group. **N.B.** Multifocal tumours (≥2 foci) of **all histological types** should be designated with "(m)", and the size of the largest focus determines the classification (as described in the TNM 7th edition). For example, if there are two foci, one 0.8cm and the other 3cm, the classification is based on the 3cm focus; i.e. pT2(m). **Exclusion** • pT1a - Papillary and Follicular carcinoma which is unifocal and ≤1cm in size, without any positive nodes – or unfavourable clinical features, treated by lobectomy • Up to 4cm non-invasive Encapsulated Follicular Variant of Papillary Thyroid Cancer (eFVPTC) with no capsular or vascular invasion (>4cm can be included at the discretion of the MDT) • Non-invasive follicular tumour with papillary-like nuclei (NIFTP) • Anaplastic, poorly differentiated or medullary carcinoma • R1/R2 Thyroidectomy • Patients with: ○ pN1b ○ M1 • Aggressive Papillary thyroid cancer with any of the following features: ○ Widely invasive ○ Poorly differentiated ○ Anaplastic

	○ Tall cell ○ Columnar cell ○ Diffuse sclerosing variants • Follicular thyroid cancer/Hürthle cell cancer with any of the following features: ○ Tumours greater than 4cm ○ Widely invasive ○ Poorly differentiated ○ Anaplastic • pT4 and pT4b (TNM7) or pT3b, pT4a and pT4b (TNM8) or macroscopic and microscopic tumour invasion of loco-regional tissues or structures • Women who are breast feeding • Patients who have CT performed with iv contrast less than 2-3 months before ablation • Previous treatment for thyroid cancer (except surgery in last 6 months) • Previous malignancies with limited life expectancy or likely to interfere with the patient's ability to be able to comply with treatment and/or follow-up at least for 5 years • Dysphagia, oesophageal stricture, active gastritis, gastric erosions, peptic ulcer, suspected reduced gastrointestinal motility • MDT decision against ablation or suitability for trial in light of severe co-morbid condition/s including: ○ Unstable angina ○ Recent myocardial infarction or cerebrovascular accident (CVA) ○ Severe labile hypertension ○ Any patient who cannot comply with radiation protection including: ▪ patients with learning difficulties ▪ patients with dementia ▪ patients with a tracheostomy that require nursing care ▪ patients requiring frequent nursing/ medical supervision
Planned number of sites:	30+
Target countries:	United Kingdom
Treatment summary:	Patients with low risk DTC who meet the eligibility criteria are randomised to: • Radioactive iodine (RAI) ablation, or • No Radioactive iodine (No-RAI) ablation

	Following surgery: • Initial neck ultrasound (no earlier than 8 weeks post-surgery) • rhTSH/hormone withdrawal • Local Tg assay and bloods No Radioactive iodine (No-RAI) ablation (arm 2): • No Radioactive iodine • TSH suppression therapy (< 0.1 mIU/L) for the duration of the trial Radioactive iodine (RAI) ablation (arm 1): • RAI ablation using Sodium [131 I] Iodide, 1.1 GBq • Post ablation scan as per standard practice • TSH suppression therapy (< 0.1 mIU/L) for the duration of the trial Both arms: • Confirmation of Optimal TSH suppression (<0.1) 2 months later • 6-9 months after ablation (Arm 1)/stimulated Tg (Arm 2): o rhTSH/hormone withdrawal stimulated Tg, neck ultrasound • Follow-up for 5 years o In the first year neck ultrasound and local Tg assay on TSH suppression therapy at 6 and 12 months o For following 4 years local Tg assay on TSH suppression therapy every 6 months and neck ultrasound every 12 months
Anticipated duration of recruitment:	6-7 years
Duration of patient follow-up:	All patients will be followed for five years (timed from the 6-9 month visit) with protocol-prescribed visits, then as per routine practice.
Definition of end of trial:	11 years after randomisation of the last patient onto the trial

1.2. Trial Schema

Key
THW=Thyroid Hormone Withdrawal;
rhTSH=recombinant human Thyroid Stimulating Hormone;
TSHST=Thyroid Stimulating Hormone suppression therapy;
TFTs=Thyroid Function Tests;
AE=Adverse Events



Please refer to the protocol for detailed information on treatment and assessments. At any time point, additional tests are allowed at the clinician's discretion.

2. Introduction

2.1. Background

2.1.1. Epidemiology

There are approximately 2000 new cases of thyroid cancer each year in the UK (3.5 per 100,000) and in 2010 over 40,000 cases in the United States[1,2]. Most of these are differentiated thyroid cancer (DTC: papillary 80% and follicular 15%), and the prognosis is generally very good, with survival rates exceeding 90-95%[3].

Most patients with thyroid cancer are women (almost three times the number of male patients), many are relatively young (30-50 years) and almost half of all new cases diagnosed are in people aged under 50[1].

2.1.2. Current standard treatment and associated issues

After diagnosis, a majority of patients are treated with three modalities - surgery, radioactive iodine (RAI) ablation and Thyroid Stimulating Hormone (TSH) suppression therapy.

Surgery is the recommended initial treatment, and involves total removal of the thyroid gland for most patients with DTC measuring >1cm in size[4]. Post surgery, the majority of patients are given RAI ablation, (usually 3.7 GBq) followed by TSH suppression therapy.

The role of RAI ablation is to destroy any remaining normal thyroid to facilitate early detection of recurrent disease, through serial measurements of thyroglobulin (Tg) levels, and also to destroy any thyroid cancer cells, thus reducing the risk of a recurrence in the future[4,5]. Although there is no clear evidence that adding RAI ablation to total thyroidectomy (TT) and TSH suppression therapy improves outcome in low risk patients, this still remains common practice in the majority of centres in Europe and the United States.

The evidence for RAI ablation is based on studies which show a benefit for recurrence and survival[4, 6]. A systematic review of RAI ablation in well-differentiated cancer was reported in 2004 and updated in 2008 with additional studies[3,7]. The review was based entirely on observational studies which often involved retrospective review of patient records. The authors concluded that RAI ablation was associated with a small but statistically significant reduction in the risk of distant metastatic recurrence among all patients (2%, 95% CI 1 to 4%), but there was no consistent effect on thyroid cancer mortality or recurrence in early stage disease. They particularly noted the very low recurrence rate in patients with papillary carcinomas, which contributed to the difficultly in making firmer conclusions. The data from observational studies must be regarded with caution due to the inherent limitations and potential bias associated with non-randomised studies.

RAI ablation could represent over-treatment in many low risk patients. For example, Hay and colleagues provide several reasons for not routinely using RAI ablation[8]; including that there is a lack of robust evidence that it is effective (i.e. no randomised

trials) and there are short and long term side effects associated with exposure to radioactive substances[8].

2.1.3. Administered activity of RAI for ablation – results from randomised trials

Preliminary results from two large randomised trials indicate that an administered activity of 1.1 GBq Sodium [131 I] Iodide (RAI) is associated with a similar ablation success rate as the standard 3.7 GBq[9,10]. Final results for these trials are now available. The IoN trial, in low risk patients, is the next stage in determining the most appropriate management for many thyroid cancer patients, by assessing whether omitting RAI ablation, with its unproven benefits and recognised side effects, compromises the high cure rates, low recurrence rates, health related quality of life and other health outcomes.

2.1.4. Justification for the proposed trial

Authors of the guidelines from the American Thyroid Association were unable to recommend either for or against RAI ablation in several specified subgroups of patients, including those similar to patients who would be eligible for the IoN trial[4]. Similarly, the UK guidelines make clear that the evidence on RAI ablation comes only from observational studies because there are no randomised trials[5].

The IoN trial will compare RAI ablation with no ablation, when all patients have had a total thyroidectomy plus TSH suppression therapy (standard practice). There is general agreement that a randomised trial of this type would resolve the issue over whether RAI ablation is beneficial and necessary in low risk patients[6,11], with eligibility characteristics specified in section 6.2 (Patient Eligibility) Potential benefits

There are 4 key areas of potential benefits to patients or the health service provider if RAI ablation could be avoided:

1) No need for hospital isolation or attendance and significant post treatment safety restrictions

Most patients with thyroid cancer are women (almost three times the number of male patients), and many are relatively young (30-50 years) and are therefore likely to have young children and be employed. Treating these patients therefore can also have a significant impact on their families. There is a clear value to patients in avoiding the inconvenience of a treatment including hospital isolation for 1-3 days. Also, importantly the RAI ablation must be followed by varying periods of ongoing radiation protection restrictions to be followed at home after discharge - in particular avoiding close contact with children.

2) No short and long term side effects of RAI ablation

RAI ablation is associated with several side effects observed after treatment. Although not very common, and depending on the activity of radioiodine used, they can include transient neck swelling with discomfort, pain and pressure symptoms, altered taste, sialadenitis in the early phase, and permanent dry mouth with increased risk of dental caries and, rarely, lachrymal duct damage as late side effects[12-14].

There is also consistent evidence that patients who have RAI ablation are at an increased risk of developing a second primary tumour in later life when compared with

the general population. For example, an analysis of 29,456 thyroid cancer patients in the United States showed an increased risk of 11% (95% CI 6 to 15%) compared to the expected risk, and the effect was particularly noticeable for cancers of the breast, prostate and kidney, and leukaemia[15]. It is plausible that some or all of this excess risk was not due to RAI ablation but a shared association between thyroid cancer and other cancers. This was addressed in a subsequent report of practically the same dataset, which analysed groups separately according to whether they had RAI ablation or not[16]. The risk of developing a second primary tumour (not thyroid cancer) was significantly higher in the RAI ablation treated group versus the untreated group; relative risk 1.16, 95% CI 1.05 to 1.27, p<0.05.

The risk of a second primary will depend on the administered activity of radioiodine, and authors of one large study estimated that for every increase of 1 GBq, the absolute excess risk increases by 14.4 per 10,000 patients per year for a new solid tumour, and 0.8 per 10,000 for leukaemia[17]. Although the absolute risk might be considered by some to be relatively small, it is a real risk which is avoidable if RAI ablation is not used at all in low risk patients.

3) Quality of Life (QOL)

Patients who have RAI ablation may get early side effects mentioned above affecting their quality of life. They will also need to modify their diet for two weeks before RAI ablation and strictly follow a low iodine diet.

4) Cost savings to the NHS (if RAI ablation was shown not to be beneficial to patients)

In addition to benefits for patients, there would also be a significant cost saving to the NHS (or other health service provider) if a large proportion of patients do not need RAI ablation, including the cost of treatment, hospital stay in isolation, and treating side effects, if they occur.

2.1.5. Potential risks

Even among patients who have initial RAI ablation either with 3.7 GBq or 1.1 GBq, some require another treatment with radioiodine sometime later because of a recurrence. The most important potential risk is that a patient who does not have RAI ablation might be at a higher chance of developing a recurrence in the subsequent years.

The recurrence rate among patients with differentiated thyroid cancer is low. In a retrospective review of 660 patients with papillary carcinomas and no residual disease from 30 Canadian sites, the relapse-free survival rate at 5 years was about 90%[18]. Among 2,512 low-risk patients with papillary carcinomas from a single site in the United States, only 15% had a recurrence after 30 years and the thyroid cancer death rate was 1%[19]. Recently, Ross et al. reported results from the follow-up of 611 patients with papillary microcarcinomas who were disease-free after initial surgery, with or without RAI ablation, after a median of 4 years[11]. Among patients who were node-negative, the proportions that had a recurrence were 3% (total or near total thyroidectomy, n=345), 6% (RAI ablation, n=159), and 2% (No-RAI ablation, n=317). The 5-year disease-free survival was greater than 90% in all of these groups. Several observational studies have been pooled together in a systematic review, by Sawka and colleagues[7], and they estimate that the 10 year recurrence rate in patients with

papillary carcinomas is 9.3% (any recurrence), 7.3% (loco-regional recurrence) and only 1.3% (metastatic disease). Thyroid cancer mortality is therefore not a major consideration in this patient subgroup.

Recent well designed retrospective studies involving large numbers of patients and modern investigational methods are even more reassuring. They suggest that after proper case selection and with current follow up strategies low risk DTC patients can be safely spared RAI ablation not only after total thyroidectomy but also after lobectomy. The recurrence rates are extremely low (2.3% after TT and 4 % after lobectomy), and the vast majority of them are still cured after additional therapy without compromising survival. Selected cases of intermediate risk DTCs also have similar outcomes without RAI ablation[20-24].

In IoN only highly selected cases after total thyroidectomy will be included.

Patients will have stringent follow up for 5 years with routine Tg measurements while on TSH suppression therapy (after stimulated Tg at 6-9 months) and neck ultrasound which is the internationally recommended approach for low risk patients[25,26]. The majority of the recurrences will be detectable within 3-5 years of initial treatment, using modern diagnostic techniques. Sensitive Tg will be done every 6 months, and more importantly an annual neck ultrasound (with or without Fine Needle Aspiration Cytology (FNAC)) will be employed in this trial. This is more frequent than current standard practice and is mandatory for detection of recurrence at the earliest possible stage[4,25,27].

The few patients who are expected to have a recurrence would be treated at the earliest possible time. The treatment modality would depend on the extent and location of any recurrent disease. This is part of normal practice, even with patients who have had RAI ablation and recurred, and is associated with a high cure rate.

3. Trial Design

Randomised non-blind non-inferiority phase II/III multicentre trial in low risk patients with differentiated thyroid cancer (DTC).

Patients with low risk DTC who have had a R0 total thyroidectomy (bilateral level VI dissection is recommended in appropriate cases, see section 6.4 (Considerations for inclusion into the IoN trial)) and meet the inclusion/exclusion criteria will be randomised into the trial.

3.1. Interventions

RAI ablation using an administered activity of 1.1 GBq versus no ablation. All patients have a total thyroidectomy plus TSH suppression therapy, as per standard practice.

3.2. Trial objectives

Primary objectives

Phase II: to determine whether the patient accrual rate is high enough for a larger phase III trial to be feasible. This will be assessed by the funder Cancer Research UK.

Phase III: to evaluate whether the disease-free thyroid cancer survival (histologically confirmed structural loco-regional recurrent or residual disease and also distant recurrence, or death from thyroid cancer) among patients not given RAI ablation is no worse than those who do have RAI ablation.

Secondary objectives

Phase III:

- To compare disease-free survival (local/distant recurrence, residual disease, or death from any cause) between the arms;
- To compare overall thyroid cancer mortality between the two arms
- To compare the incidence of loco-regional disease in the two arms
- To compare the incidence of distant recurrence and biochemical recurrence between the two arms
- To compare the proportion of patients who have further surgery
- To compare the proportion of patients who have further radioiodine
- To examine the number of patients who have a delayed radioiodine in the no-RAI ablation group
- To compare additional investigations required to confirm recurrence in both arms
- To compare health-related quality of life between patients who do or do not receive RAI ablation
- To compare adverse events between patients who do or do not receive RAI ablation
- The incidence of second primary tumours (after long-term follow-up)

- To examine the cost-effectiveness of a treatment policy with or without RAI ablation, including the costs of treating side effects and future recurrences
- Correlation of recurrence rate and biomarkers (e.g. BRAF) in both arms

3.3. Trial outcome measures

Primary outcome measures

Phase II: monthly accrual rate

Phase III: Disease-free thyroid specific survival (i.e. no local or distant recurrence, and did not die from thyroid cancer)

Secondary outcome measures

- Mortality (cause and date of death)
- Occurrence of loco-regional recurrence or metastatic disease
- Stage of cancer at the time of recurrence, and the ability to treat this successfully
- Adverse events graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
- Health-related quality of life using QLQ-C30, QLQ-H&N35 and the EQ5D
- Further neck surgery
- Further RAI ablations, and the reasons for this
- Cost-effectiveness

3.4. Trial activation

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

- Research Ethics Committee approval
- Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA)
- **‘**Adoption’ into NIHR portfolio
- NHS permission
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

4. Selection of Sites/Site Investigators

4.1. Site selection

In this protocol trial **"Site"** refers to the hospital or site where trial-related activities are conducted.

Sites must be able to comply with:

- Trial treatments, imaging, follow-up schedules and all requirements of the trial protocol
- Requirements of the Research Governance Framework and the Medicines for Human Use (clinical trials) Act (SI 2004/1031 and all amendments)
- Data collection requirements, including adherence to CRF submission timelines as per section 11.3 (Timelines for data return)
- Monitoring requirements, as outlined in protocol (section 14 (Trial Monitoring and Oversight) and trial monitoring plan)

4.1.1. Selection of Principal Investigator and other investigators at sites

Sites must have an appropriate Principal Investigator (PI) i.e. a health care professional authorised by the site, ethics committee and regulatory authority to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI. All investigators must be medical doctors and have experience of treating differentiated thyroid cancer.

4.1.2. Training requirements for site staff

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

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). An up-to-date, signed copy of the CV with evidence of up-to-date GCP training (or copy of GCP certificate) for the Principal Investigator must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing Institution, or 2 yearly where the Institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

4.2. Site initiation and activation

4.2.1. Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation, with the site which the PI, site research team and nuclear medicine representative must attend.

The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site by a site visit or teleconference. Re-initiating sites may be required where there has been a significant delay between initiation and enrolling the first patient, as per monitoring plan.

4.2.2. Required Documentation

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

- Trial specific Site Registration Form (identifying relevant local staff)
- All relevant institutional approvals A signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually a NHS Trust/Health Board)
- Where applicable a research ARSAC certificate held by Nuclear Medicine
- A completed site delegation log, initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- Completed site contacts form (with contact information for all members of local staff)
- A copy of the PIs current CV, signed and dated (with documented up to date GCP training, or copy of GCP training certificate)

4.2.3. Site activation letter

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

Once the site has been activated by UCL CTC, the PI is responsible for ensuring:

- Adherence to the most recent version of the protocol
- All relevant site staff are trained in the protocol requirements
- Appropriate recruitment and medical care of patients in the trial
- Timely completion and return of CRFs (including assessment of all adverse events)
- Prompt notification and assessment of all serious adverse events
- That the site has facilities to provide **24 hour medical advice** for trial patients

5. Informed Consent

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

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

Sites must assess a patient's ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the trial. Consideration must also be given to whether access to a local interpreter will be feasible/available for patients at all hospital visits attended for the trial, and especially for those randomised to receive ablation, when they are in isolation.

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

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

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

Site staff are responsible for:

- checking that the correct (current approved) version of the patient information sheet and consent form are used
- checking that information on the consent form is complete and legible
- checking that the patient has initialled all relevant sections and signed and dated the form
- Checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient
- Checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.)
- Following randomisation, giving the patient a copy of their signed consent form, patient information sheet and patient contact card

- Following randomisation, adding the patients' trial number to all copies of the consent which should be filed in the patients' medical notes and investigator site file.

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

6. Selection of Patients

6.1. Screening Log

A screening log must be maintained and appropriately filed at site. Sites should record each patient screened for the trial and the reasons why they were not randomised in the trial if this is the case. The log must be sent to UCL CTC when requested.

Patients discussed at MDT meetings or considered by investigators must be added to the screening log regardless of whether they subsequently enter the trial.

6.2. Patient Eligibility

There will be no exception to the eligibility requirements at the time of randomisation. Queries in relation to the eligibility criteria should be addressed prior to randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

Refer to sections 6.3 (Recommended surgery) and 6.4 (Considerations for inclusion into the IoN trial) for guidance and definition around surgery and inclusion into IoN.

TNM eligibility should be assessed against TNM 7th edition (2009) or TNM 8th edition (2018) using the tumour sample taken at surgery.

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

Patients must give written informed consent before any trial specific screening investigations may be carried out. Refer to section 9.3 (Pre-randomisation Assessments) for the list of assessments and procedures required to evaluate the suitability of patients prior to entry.

6.3. Thyroid surgery

6.3.1. Recommended surgery

In addition to total thyroidectomy, patients with papillary thyroid cancer (PTC) or mixed papillary and other histologies, or those aged over 45 years, who have tumours greater than 2cm (especially T3 tumours) may undergo a prophylactic bilateral or ipsilateral central compartment node dissection (CCND-P). This should be at the discretion of the surgeon who has the expertise to undertake such procedures safely.

This should be carefully considered in the light of available surgical expertise because complication rates are higher. CCND-P should only be considered in units who perform this routinely and have acceptable complication rates according to local or national audits such as conducted by the British Association of Endocrine and Thyroid Surgeons; all other sites should avoid this.

For patients with PTC, pre-operative ultrasound assessment of central compartment and intra-operative assessment of the central compartment are strongly recommended. If these suggest nodal involvement in the central compartment then a bilateral therapeutic CCND (CCND-T) level VI dissection is strongly recommended, keeping in mind the limitations of these assessments.

It is expected that most sites will have nominated surgeons for node dissections and access to the necessary surgical expertise for these cases. MDT's should consider identifying one or two surgeons who will be performing CCND (P and T) for the trial if possible.

For uniformity current Expert Surgical Opinion suggest the following as a guide for CCND[28]:

> "Central neck dissection, bilateral: Removal of the prelaryngeal, pretracheal, and both the right and left paratracheal nodal basins.
>
> Central neck dissection, unilateral: Removal of the prelaryngeal, pretracheal, and one paratracheal nodal basin."

6.3.2. Staging

A patient can only be considered N0 if all lymph nodes retrieved are assessed pathologically as node negative. Patients with nodal involvement inside the level VI compartment will be classified as pN1a.

Patients who do not undergo ipsilateral or bilateral level VI dissection will be classified as NX.

Patients with nodal involvement outside the level VI compartment are classed as N1b and will not be eligible for the trial.

6.4. Considerations for inclusion into the IoN trial

It is acknowledged that in many sites prophylactic bilateral or ipsilateral dissection will not be routine. Patients are still eligible for IoN if a one stage or two stage total thyroidectomy has been performed with no residual disease present (R0 resection).

It is also acknowledged that some sites may choose not to enter patients with T3 tumours.

6.4.1. Patient Inclusion Criteria

TNM eligibility is assessed against TNM7 (7th edition 2009) or TNM8 (8th edition 2017, in use in the UK from 01/01/2018).

Eligibility Criteria using TNM7:

Inclusion criteria:

- Histological confirmation of well differentiated thyroid carcinoma: MDT decision for inclusion based on overall clinico-pathological assessment is critical.

- R0 total thyroidectomy (in one or two stages, no residual disease present; Rx at the discretion of the MDT) within the last 6 months
- Negative pregnancy test in women of child bearing potential
- Aged 16 or over
- WHO performance status 0 – 2, self-caring
- Histological confirmation of differentiated thyroid carcinoma:MDT decision for inclusion based on overall clinico-pathological assessment
- Papillary thyroid cancer (PTC):
  - Non aggressive histological features (small foci of aggressive histology allowed at the discretion of the MDT)
  - pT1a (≤1cm) unifocal with positive level VI lymph nodes (pN1a)
  - pT1a(m): all individual foci ≤1cm
  - pT1b and pT1b(m): >1-2cm
  - pT2 and pT2(m): >2-4cm
  - pT3 and pT3(m): >4cm confined to the thyroid
  - pT3 R0 +/- (m): any size with minimal ETE if recommended by the MDT
  - pN0
  - pN1a
  - pNX
- Follicular thyroid cancer (FTC) (including oncocytic or Hürthle cell cancer):
  - minimally invasive FTC –which are considered low risk and are recommended by the specialist MDT based on overall clinico-pathological assessment
    - pT1b and pT2: >1-4cm intrathyroidal
    - pT3 R0:any size up to 4 cm with minimal ETE if recommended by the MDT
- Histological material available for Central Review (see section 9.7)
- Willing to use contraception for the duration of the trial until 6 months post radioiodine treatment (for females) or 4 months post treatment (for males) (see section 6.4.2), if allocated to the ablation group.

NB: Multifocal tumours (≥2 foci) of **all histological types** should be designated with "(m)", and the size of the largest focus determines the classification (as described in the TNM 7th edition). For example, if there are two foci, one 0.8cm and the other 3cm, the classification is based on the 3cm focus; i.e. pT2(m).

Exclusion criteria:

- pT1a - Papillary and Follicular carcinoma which is unifocal and ≤1cm in size, without any positive nodes or unfavourable clinical features, treated by lobectomy.
- Up to 4cm non-invasive Encapsulated Follicular Variant of Papillary Thyroid Cancer (eFVPTC) with no capsular or vascular invasion (>4 cm can be included at the discretion of the MDT)

- non-invasive follicular tumour with papillary-like nuclei (NIFTP)
- Anaplastic, poorly differentiated or medullary carcinoma
- R1 or R2 thyroidectomy
- Patients with:
  - pN1b
  - M1
- Aggressive Papillary thyroid cancer with any of the following features:
  - Widely invasive
  - Poorly differentiated
  - Anaplastic
  - Tall cell
  - Columnar cell
  - Diffuse sclerosing variants
- Follicular thyroid cancer/Hürthle cell cancer with any of the following features:
  - Tumours greater than 4cm
  - Widely invasive
  - Poorly differentiated
  - Anaplastic
- Incomplete resection or lobectomy
- pT4a and pT4b or macroscopic and microscopic tumour invasion of loco-regional tissues or structures
- Pregnant women or women who are breast feeding
- Patients who have had CT performed with iv contrast less than 2-3 months before ablation
- Previous treatment for thyroid cancer (except surgery in last 6 months)
- Previous malignancies with limited life expectancy or likely to interfere with the patient's ability to be able to comply with treatment and/or follow-up for at least 5 years
- The following GI conditions: dysphagia, oesophageal stricture, active gastritis, gastric erosions, peptic ulcer, suspected reduced gastrointestinal motility
- MDT decision against ablation or suitability for trial in light of severe co-morbid condition/s including:
  - Unstable angina
  - Recent myocardial infarction or cerebrovascular accident (CVA)
  - Severe labile hypertension
  - Any patient who cannot comply with radiation protection including:
    - patients with learning difficulties
    - patients with dementia
    - patients with a tracheostomy that require nursing care
    - patients requiring frequent nursing/ medical supervision

Eligibility Criteria using TNM8:

Inclusion criteria:

- Histological confirmation of well differentiated thyroid carcinoma: MDT decision for inclusion based on overall clinico-pathological assessment is critical.
- R0 total thyroidectomy (in one or two stages, no residual disease present; Rx at the discretion of the MDT) within the last 6 months
- Negative pregnancy test in women of child bearing potential
- Aged 16 or over
- WHO performance status 0 – 2, self-caring
- Histological confirmation of differentiated thyroid carcinoma:MDT decision for inclusion based on overall clinico-pathological assessment
- Papillary thyroid cancer (PTC):
  - Non aggressive histological features (small foci of aggressive histology allowed at the discretion of the MDT)
  - pT1a (≤1cm) unifocal with positive level VI lymph nodes (pN1a)
  - pT1a(m): all individual foci ≤1cm
  - pT1b and pT1b(m): >1-2cm
  - pT2 and pT2(m): >2-4cm
  - pT3a and pT3a(m): >4cm confined to thyroid
  - pT1a/1b/2/3 (where minimal microscopic extra thyroidal extension (ETE) does not change the T score) +/- (m): any size with minimal ETE if recommended by the MDT
  - pN0
  - pN1a
  - pNX
- Follicular thyroid cancer (FTC) (including oncocytic or Hürthle cell cancer):
  - minimally invasive FTC –which are considered low risk and are recommended by the specialist MDT based on overall clinico-pathological assessment
    - pT1b and pT2: >1-4cm intrathyroidal
    - pT1a/1b/2/3a (where minimal microscopic ETE does not change the T score): any size up to 4 cm with minimal ETE if recommended by the MDT
- Histological material available for Central Review (see section 9.7)
- Willing to use contraception for the duration of the trial until 6 months post radioiodine treatment (for females) or 4 months post treatment (for males) (see section 6.4.2), if allocated to the ablation group.

Exclusion criteria:

- pT1a - Papillary and Follicular carcinoma which is unifocal and ≤1cm in size, without any positive nodes or unfavourable clinical features, treated by lobectomy.
- Up to 4cm non-invasive Encapsulated Follicular Variant of Papillary Thyroid Cancer (eFVPTC) with no capsular or vascular invasion (>4 cm can be included at the discretion of the MDT)
- non-invasive follicular tumour with papillary-like nuclei (NIFTP)
- Anaplastic, poorly differentiated or medullary carcinoma
- R1 or R2 thyroidectomy
- Patients with:
  - pN1a with level VII involvement
  - pN1b
  - M1
- Aggressive Papillary thyroid cancer with any of the following features:
  - Widely invasive
  - Poorly differentiated
  - Anaplastic
  - Tall cell
  - Columnar cell
  - Diffuse sclerosing variants
- Follicular thyroid cancer/Hürthle cell cancer with any of the following features:
  - Tumours greater than 4cm
  - Widely invasive
  - Poorly differentiated
  - Anaplastic
- Incomplete resection or lobectomy
- pT3b, pT4a and pT4b or macroscopic and microscopic tumour invasion of loco-regional tissues or structures
- Pregnant women or women who are breast feeding
- Patients who have had CT performed with iv contrast less than 2-3 months before ablation
- Previous treatment for thyroid cancer (except surgery in last 6 months)
- Previous malignancies with limited life expectancy or likely to interfere with the patient's ability to be able to comply with treatment and/or follow-up for at least 5 years
- The following GI conditions: dysphagia, oesophageal stricture, active gastritis, gastric erosions, peptic ulcer, suspected reduced gastrointestinal motility
- MDT decision against ablation or suitability for trial in light of severe co-morbid condition/s including:
  - Unstable angina

- Recent myocardial infarction or cerebrovascular accident (CVA)
- Severe labile hypertension
- Any patient who cannot comply with radiation protection including:
  - patients with learning difficulties
  - patients with dementia
  - patients with a tracheostomy that require nursing care
  - patients requiring frequent nursing/ medical supervision

6.4.2. Pregnancy and Birth Control

Pregnant women or women who are breast feeding are not eligible for IoN.

Pregnancy Testing

All women of childbearing potential (WCBP) who are at risk of becoming pregnant must undergo a pregnancy test (blood or urine) within the 7 days prior to randomisation and on the day of ablation. Departmental standard procedures and local IRMER (Ionising Radiation Medical Exposures Regulations) employer's procedure must be followed.

A woman of childbearing potential is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who has not:

- undergone a hysterectomy or bilateral oophorectomy/ salpingectomy
- been postmenopausal for 24 consecutive months (i.e. who has had menses at any time in the preceding 24 consecutive months without an alternative medical cause)

Contraceptive Advice

Due to the effects of radioiodine treatment during pregnancy and lactation, female patients allocated to the ablation group (arm 1) must consent to use one of the following acceptable methods of contraception from informed consent to at least 6 months following the radioiodine ablation (a small risk of spontaneous abortion may persist for up to 1 year after high activity ^{13l}I ablation[5]).

Male patients allocated to the ablation group (arm 1) with partners of childbearing potential must consent to use acceptable methods of contraception for at least 4 months following radioiodine ablation and should not father a child during this time.

Pregnancy guidance is taken from the British Thyroid association guidelines 2007[5].

Acceptable methods of effective contraception for this trial are:

- Established use of oral, injected or implanted hormonal methods of contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository). The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:

  - Failure rates indicate that, when used alone, the diaphragm and condom are **not** highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection
  - However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and must not be used alone
- Male sterilisation (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomised male partners must be the sole partner for that patient. Please note that sterilisation is not usually regarded as completely reliable enough on its own to ensure that pregnancy can never occur
- Absolute and continuous abstinence: When this is in line with the preferred and usual lifestyle of the patient. Please note that periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)

The method(s) of contraception used must be recorded in the patient medical notes.

If a patient or the partner of a male trial patient allocated to the ablation group (arm 1) becomes pregnant during the trial UCL CTC must be informed immediately (See section 12 (Pharmacovigilance) for details on the reporting procedure).

7. Randomisation procedures

Patients will be randomised using the minimisation method, stratified according to:

- recruiting site
- patient age (<20, 20-45, and >45 years)
- T stage (T1, T2, T3 and T1a(m))
- N stage (N0, N1a and NX)

7.1. Randomisation

Patient randomisation will be undertaken centrally at UCL CTC and this must be performed prior to commencement of any trial treatment. Patient randomisation can be completed by telephone or by faxing the eligibility and randomisation forms to UCL CTC.

Following surgery, pre-treatment evaluations, confirmation of eligibility (as detailed in 6, section Selection of Patients) and consent (see section 5.0; Informed Consent) of a patient, the eligibility and randomisation forms must be fully completed prior to telephoning or faxing the UCL CTC. Sites must confirm on the registration form which version of TNM was used to confirm eligibility. The eligibility criteria will either be reviewed during the randomisation telephone call, or if faxed, the forms will be reviewed and the site contacted if there are any queries.

A trial number and treatment allocation (RAI ablation or No-RAI ablation) will be assigned for the patient. UCL CTC will email confirmation of the patient's inclusion in the trial, their trial number and treatment allocation to the main contact and nuclear medicine department.

Randomisation telephone number:	+44 (0)20 7679 9880
Fax number:	+44 (0)20 7679 9871
Office hours:	09:00 to 17:00 Monday to Friday (UK Time)

Once a patient has been randomised onto the trial they must be provided with the following:

- A copy of their signed consent form and patient information sheet
- A patient contact card. Site contact details for 24 hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial

The site should then arrange a neck ultrasound scan visit date with the patient. For RAI ablation patients the site can then order 1.1 GBq Sodium [131 I] Iodide as usual, which must be administered after the ultrasound. This minor delay is of no clinical consequence in this very low risk group.

For all patients, all tumour sample slides used in the diagnosis of thyroid cancer, the original pathology report and IoN histology review submission form should be sent for

central review within a month of randomisation (see section 9.7 (Central Histological Review).

8. Trial Treatment

8.1. Treatment summary

For the purpose of this protocol, the IMP is Sodium [131 I] Iodide (Radioactive Iodine; RAI) and the NIMPs are, T3/T4 and rhTSH.

Radioactive iodine (RAI) ablation using an activity of 1.1 GBq RAI is given in one trial group and there is no ablation (No-RAI ablation) in the other group. All patients receive TSH suppression therapy (T3/T4) after surgery as per routine practice. rhTSH will be given to patients in sites where it is standard practice. Patients receiving rhTSH do not need to undergo hormone withdrawal.

Patients should not be given a second dose of RAI in the RAI ablation group, or an ablation in the No-RAI ablation group, unless there is confirmed evidence of recurrence (see section 10 (Residual/Recurrent disease)). If either of these occurs, the data must be captured on a case report form, along with the reasons for the ablation.

8.2. Trial Treatment Details

8.2.1. Radioactive iodine (RAI) ablation

RAI is licensed and will be administered at an activity of 1.1 GBq (sites usually allow ±10%) to patients in the RAI ablation arm. Sourcing of RAI will be the responsibility of the site.

Pregnant women or women who are breast feeding must not be administered RAI. The pregnancy and breast feeding status of female patients must be checked prior to administration of RAI.

Patients receiving ablation should be advised by the Nuclear Medicine department and clinician in charge of the patient about their radiation risks, need for isolation, timing of discharge from the hospital and post discharge safety precautions to be followed, as per site standard practice.

8.2.2. Thyroid Stimulation

Patients will undergo either thyroid hormone withdrawal or have rhTSH prior to the stimulated Tg measurements according to local site policy. It is recommended that rhTSH be used, following the HiLo trial results[9], because of the advantages of improved quality of life (compared to temporarily stopping thyroid hormone therapy) and (in the ablation group) faster renal clearance of RAI. For patients randomised to receive RAI ablation, the neck ultrasound must be done before administration of RAI and preferably at least 8 weeks after surgery.

For patients undergoing thyroid hormone withdrawal T4 must be withdrawn 4 weeks before the stimulated Tg measurement and ablation. Patients may switch to T3 at this time (as is routinely done). T3 should then be discontinued 2 weeks before the stimulated Tg measurements.

Thyroid hormone withdrawal may induce symptomatic hypothyroidism, which may result in lethargy, cognitive impairment or depression. Recommencement of TSH suppression therapy should not begin earlier than 2 days after RAI ablation. Recommencement of TSH suppression therapy after stimulated Tg, for the No-RAI ablation patients can resume the same day (see section 9 (Assessments) for further details).

8.2.3. TSH Suppression Therapy

TSH suppression will be maintained throughout the trial period with the following aims:

1) Maintain TSH <0.1 mIU/L as this is one important modality of treatment. If TSH is not < 0.1 mIU/L dose adjustment is required.
2) Free T3 is maintained within normal range (in some sites if T3 is not routinely measured satisfactory T4 level is acceptable according to local practice).
3) Keep the patient euthyroid

This is to avoid any impact of variable TSH suppression therapy on recurrence rate during the course of the trial, although for low risk thyroid cancers this degree of suppression may not be required[4].

Trial patients are going to be followed up for long term survival and recurrence and it is suggested that after 5 years national guidelines are followed[4,5].

8.2.4. Nuclear Medicine responsibilities

Radioactive materials must be handled as per local practice.

8.2.5. IMP accountability

Accountability for RAI at participating sites is the responsibility of the Principal Investigator who may delegate this responsibility to the nuclear medicine department or other appropriately qualified personnel. The responsible person will ensure that RAI is used only in accordance with this protocol and that appropriate records are maintained. A copy of the Radioactive Iodine (Sodium Iodine) accountability logs will be requested by UCL CTC for applicable trial patients. See also section 14.1(Central Monitoring).

The site nuclear medicine department must maintain accountability records for RAI administered to patients including receipt, dispensing, and storage conditions. Template accountability forms will be supplied, however, sites are permitted to use their own accountability records providing the same information is captured, as a minimum. Such in-house records must be submitted to UCL CTC for review and authorisation for use prior to patient enrolment.

8.3. Management after treatment withdrawal

Subsequent treatment will be at the discretion of the treating clinician.

9. Assessments

9.1. Low iodine diet

Patients randomised to receive RAI ablation should be put on a low iodine diet for 2 weeks before the day of ablation. Medications, complimentary medicine and other food substances that contain iodine (such as multi-mineral supplements and kelp) should be avoided, except thyroid hormone replacement. A low iodine diet sheet will be supplied to provide advice and guidance for patients in the RAI ablation arm.

If patients are taking complimentary medicine, they should seek advice from their hospital clinician.

9.2. Neck Ultrasound

The ultrasound scan is an important test for baseline and for future monitoring to exclude residual and recurrent disease.[29] The operator should take note of any areas of thyroid remnant or recurrence, and also record the locations of possible malignant lymph nodes as well as benign nodes.

All ultrasound scans must be performed by an experienced operator.

The initial neck ultrasound scan (all patients):

- Should be performed preferably at least 8 weeks after surgery.

9.3. Pre-randomisation Assessments

Patients must give written informed consent before any trial specific investigations may be carried out. The following assessments or procedures are required to evaluate the suitability of patients for the trial:

- Histological confirmation of differentiated thyroid carcinoma and assessment of tumour characteristics (invasion, aggressiveness)
- TNM staging; 7th edition (2009) or 8th edition (2017)

Within 14 days prior to randomisation:

- Written informed consent

Within 7 days prior to randomisation:

- Assessment of WHO performance status
- Pregnancy test (urine or blood) in women of child bearing potential
- Clinical exam
- Baseline bloods and thyroid function tests as per site standard practice
- EORTC QLQ-C30, QLQ-H&N35 and EuroQoL EQ-5D questionnaires to be completed
- Assessment of adverse events

- Current medications (including complimentary medications)

9.4. Assessments during treatment

The following investigations must be performed following randomisation.

9.4.1. Ablation (Arm 1)

The following order of events should be observed in preparation for ablation administration and blood sampling for stimulated Tg test.

For patients having thyroid hormone withdrawal

1) Neck ultrasound**
2) Thyroid hormone withdrawal with T3 withdrawal beginning at least 2 weeks prior to RAI ablation (patients receiving T4 must first switch to T3 prior to withdrawal – see section 8.2.2 - Thyroid Stimulation)
3) ON THE DAY OF ABLATION AND INITIAL STIMULATED Tg TEST:
   a) The following may be done in any order:
      - QLQ-C30, QLQ-H&N35 and E5-QD questionnaires to be completed
      - Pregnancy test (urine or blood) in women of child bearing potential, prior to ablation
      - Blood samples for TSH, thyroid function tests (free T3, free T4), Tg Antibody (Ab) and Tg assay
      - Blood sample for stimulated Tg test*
   b) RAI ablation
4) Resume TSH suppression therapy (targeting TSH <0.1 mIU/L) 2 days after ablation
5) Post ablation scan 3-10 days after ablation (according to Site's standard practice)

**Blood samples may be taken post ablation on day 4 or 5 if this is local practice.*

***Neck ultrasound can be completed prior to or after thyroid hormone withdrawal.*

For patients having rhTSH (no thyroid hormone withdrawal required)

1) Neck ultrasound**
2) rhTSH on days 1 & 2
3) ON DAY OF ABLATION AND INITIAL STIMULATED Tg TEST (DAY 3):
   a) The following may be done in any order:
      - QLQ-C30, QLQ-H&N35 and E5-QD questionnaires to be completed
      - Pregnancy test (urine or blood) in women of child bearing potential, prior to ablation
      - Blood samples for TSH, thyroid function tests (free T3, free T4), Tg Antibody (Ab) and Tg assay
      - Blood sample for stimulated Tg test*
   b) RAI ablation

4) Post ablation scan 3-10 days after ablation (according to sites standard practice)

**Blood samples may be taken post ablation on day 4 or 5 if this is local practice.*

***Neck ultrasound can be completed prior to or after rhTSH administration.*

9.4.2. No ablation (Arm 2)

The following order of events should be observed in preparation for blood sampling for stimulated Tg test.

For patients having thyroid hormone withdrawal

1) Neck ultrasound**
2) Thyroid hormone withdrawal with T3 withdrawal beginning at least 2 weeks prior to stimulated Tg test (patients receiving T4 must first switch to T3 prior to withdrawal – see section 8.2.2 - Thyroid Stimulation)
3) ON THE DAY OF INITIAL STIMULATED Tg TEST:
   a) The following may be done in any order:
      - QLQ-C30, QLQ-H&N35 and E5-QD questionnaires to be completed
      - Blood samples for TSH, thyroid function tests (free T3, free T4), Tg Antibody (Ab) and Tg assay
      - Blood sample for stimulated Tg test
   b) Resume TSH suppression therapy (targeting TSH <0.1 mIU/L)

***Neck ultrasound can be completed prior to or after thyroid hormone withdrawal.*

For patients having rhTSH (no thyroid hormone withdrawal required)

1) Neck ultrasound**
2) rhTSH on days 1 & 2
3) ON THE DAY OF INITIAL STIMULATED Tg TEST (DAY 5):
   a) The following may be done in any order:
      i) QLQ-C30, QLQ-H&N35 and E5-QD questionnaires to be completed
      ii) Blood samples for TSH, thyroid function tests (free T3, free T4), Tg Antibody (Ab) and Tg assay
      iii) Blood sample for stimulated Tg test

***Neck ultrasound can be completed prior to or after rhTSH administration.*

9.5. Assessments on completion of trial treatment

9.5.1. 2 months after initial stimulated Tg test

- Clinical Exam
- Assess patient for adverse events
- QLQ-C30, QLQ-H&N35 and E5-QD questionnaires to be completed
- Blood samples for TSH, thyroid function tests (free T3, free T4), Tg Antibody (Ab) and Tg assay

- **Adjust T4 levels to target TSH < 0.1 mIU/L as required**

9.5.2. 6-9 month after initial stimulated Tg test

The following order of events should be observed in preparation for blood sampling for stimulated Tg test. Note that the method of TSH stimulation used is not dependent upon that used previously.

For patients having thyroid hormone withdrawal

1) The following may be done in any order:
   a) Neck ultrasound
   b) Blood samples for TSH, thyroid function tests (free T3, free T4), Tg Ab and Tg assay
2) Thyroid hormone withdrawal with T3 withdrawal beginning at least 2 weeks prior to stimulated Tg test (patients receiving T4 must first switch to T3 prior to withdrawal – see section 8.2.2 - Thyroid Stimulation)
3) ON THE DAY OF STIMULATED Tg TEST:
   a) The following may be done in any order:
      i) QLQ-C30, QLQ-H&N35 and E5-QD questionnaires to be completed
      ii) Clinical Exam*
      iii) Assess patient for adverse events
      iv) Blood sample for stimulated Tg test
   b) Resume TSH suppression therapy (targeting TSH <0.1 mIU/L)

**the clinical exam and assessment of adverse events may be performed outside of the stated procedure order depending on local practice and clinic schedules.*

For patients having rhTSH (no thyroid hormone withdrawal required)

1) The following may be done in any order:
   a) Neck ultrasound
   b) Clinical Exam*
   c) Assess patient for adverse events
2) Blood samples for TSH, thyroid function tests (free T3, free T4), Tg Ab and Tg assay (day 1)
3) rhTSH (days 1 & 2)
4) ON THE DAY OF STIMULATED Tg TEST (DAY 5):
   a) The following may be done in any order:
      i) QLQ-C30, QLQ-H&N35 and E5-QD questionnaires to be completed
      ii) Blood sample for stimulated Tg test

If patients are Tg antibody positive, Tg antibody level could be used as a possible surrogate marker of recurrence, although it is not reliable (see section 10 (Residual/Recurrent disease)). No additional tests should be done routinely in this group unless at the discretion of the clinician, as ultrasound scans are being done regularly which will address this problem.

**the clinical exam and assessment of adverse events may be performed outside of the stated procedure order depending on local practice and clinic schedules.*

9.6. Assessments during follow-up (see also section 10)

All patients will be followed up every 6 months after the 6-9 month stimulated Tg test for 5 years as set out below. Note that Tg assay will be done while patients are on TSH suppression therapy.

9.6.1. Year 1

To be carried out every 6 months:

- Neck ultrasound (with or without fine needle aspirate cytology (FNAC) as required)
- Clinical examination
- Assess patient for adverse events
- Completion of QLQ-C30, QLQ-H&N35 and E5-QD questionnaires
- Blood samples for TSH, thyroid function tests (free T3, free T4), Tg Ab and Tg assay

9.6.2. Years 2-5

To be carried out every 6 months:

- Clinical examination
- Assess patient for adverse events
- Completion of QLQ-C30, QLQ-H&N35 and E5-QD questionnaires
- Blood samples for TSH, thyroid function tests (free T3, free T4), Tg Ab and Tg assay

To be carried out every 12 months:

- Neck ultrasound (with or without FNAC).

9.6.3. Additional information about follow up

The clinician and radiologist in charge will decide according to current practice (usually in conjunction with clinical assessment and/or rising Tg levels) when a FNAC is required to confirm structural recurrence or residual disease based on US assessment of thyroid bed, lymph node appearance and size as per protocol.

After 5 years of follow up, patients should be followed up according to routine practice. UCL CTC will request follow up annually, unless the patient withdraws consent. The intention is to record recurrence, new cancers and date and cause of death. Patients may also be monitored during follow up by UCL CTC via data registries e.g. NHS Digital.

The frequency and method of follow-up should help reduce concerns about the group of patients who do not have RAI ablation. A recurrence tends to be relatively slow growing in low-risk cancer patients, and the few patients who have a recurrence should be detected and treated successfully. Most loco-regional recurrences and residual

disease are detected in the first 3-5 years with current techniques. Using Tg measurement and neck ultrasound for following up low-risk patients after ablation as the initial assessment is the internationally recommended approach[4,25]. In this trial serial ultrasounds are mandatory and are being carried out for closer surveillance not to miss early structural recurrences especially in the No-RAI ablation group.

Serial Tg with suppressed TSH will be assayed in the same Site, using local cut offs as a trigger (in the ablated arm) for further investigation.

Additional US scan, FNAC, stimulated Tg, CT scan, MRI, diagnostic radioiodine scan, Tg from needle aspirates (only in rare cases of cystic nodes with rising Tg and at least 5mm in size), or PET-CT (as appropriate) would be considered by the clinician in charge according to standard local practice if a recurrence is suspected.

In the event a patient fails to attend a clinic or cannot be followed up at site all efforts should be made by the Site to contact the patient's GP to assess their condition.

9.7. Central Histological Review

Central histology review for the trial will be undertaken for all patients to confirm tumour type, staging and eligibility for IoN. Patients must consent to histological review to be eligible for the trial.

All slides used for the diagnosis of thyroid cancer and used to confirm IoN eligibility criteria should be sent for review within one month of randomisation to the following address:

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

Original stained slides should be sent by post within one month of patient randomisation and an IoN histology review submission form should be included along with a copy of the original pathology report. The pathology report must have all patient identifiers removed and patient trial number and initials added before sending to UCL CTC.

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

Histological review will be undertaken by pathologists in the Royal Hallamshire Hospital, Sheffield or Victoria Royal Infirmary, Newcastle. Slides will be returned to sites once a diagnosis has been agreed. Any diagnosis that is different to the site diagnosis will have to be agreed by the other reviewer.

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

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

9.8. Collection of Tissue for Translational Research

9.8.1. BRAF

BRAF mutation analysis particularly V600E will be performed on tumour tissue from patients consenting to this part of the translational research.

Tumour tissue (paraffin tumour blocks) will be requested for patients entered in the phase II trial when the trial moves to phase III.

10. Residual/Recurrent disease

The most common site for recurrence is loco-regional. Residual/Recurrent disease should be suspected only after considering clinical assessment, rising Tg and structural imaging such as US, usually in combination.

Tissue diagnosis (fine needle aspirate cytology [FNAC] or biopsy) triggered by the above investigations is required to confirm structural loco-regional recurrence or residual disease in IoN (this is standard practice in the UK).

Occasionally other tests such as X-rays, CT scan, radioiodine scans, PET-CT scans might be required at the discretion of the treating clinician, particularly to diagnose recurrences outside the loco-regional site where tissue diagnosis is not feasible or not done in routine practice.

There is concern about earlier diagnosis of recurrence in the RAI ablation arm because of the increased sensitivity and specificity of Tg. However, this ascertainment bias can be counteracted by mandatory requirement of an US and tissue diagnosis of structural recurrence or residual disease. This will be achieved in most cases by restricting FNAC in patients with a proven serial rise in Tg or thyroglobulin antibody (Tg Ab) to:

1) lymph nodes, which are at least 10 mm or more in size in smallest diameter, usually with sonographic appearance of malignancy
2) Nodes that have progressively increased in the previous successive US scans but is not less than 5 – 8 mm in size and/or has sonographic appearance of malignant lymph nodes
3) Thyroid bed or other soft tissue recurrences which have progressively increased in size and/or has sonographic appearance of malignancy

Most recurrences are detected in 3-5 years even without routine annual US for five years[11,27,30]. Annual US (and triggered FNAC based on mandatory size criteria as above) will even out any possible variation in the timing of the detection of recurrence in both the arms over the five year period.

As in standard UK practice an isolated rise in Tg or Tg Ab should not lead to blind radioiodine treatment or surgery for presumed but unconfirmed loco-regional recurrent disease in the absence of tissue diagnosis. Newly identified structural disease is required. This would usually lead to some intervention such as a positive FNAC or excision histology.

The Tg cut-off value for triggering investigations to look for recurrence is specific for each site. Rising Tg on serial testing is more important than a single measurement. A detectable Tg on TSH suppression therapy or stimulated Tg >2 mIU/L is usually (for immunoradiometric assay) used in ablated cases.

For No-RAI ablation cases serial rise in Tg is more important (with the same level of TSH suppression) as there is no available data. Tg doubling time may also be used both for ablated and non-ablated cases. However the ultrasound scans at 6-9 months, 6 month follow up and annual thereafter will help detect recurrent/residual disease without any significant delay. This also applies to patients with Tg antibodies.

No clinical Evidence of Disease (NED) can be defined as a suppressed serum Tg < 1 mIU/L, no detectable Tg Ab, and no structural evidence of disease on US, with or without fine needle aspiration cytology (FNAC)[30].

10.1. Distant recurrence (usual sites lung or bone)

Usually distant recurrence will be diagnosed by clinical examination, rising Tg, positive RAI scan or other structural imaging. Miliary metastases on radiology would also be accepted and would usually be confirmed by a positive radioiodine scan. Biopsy is not required, or possible, in most cases.

A radioiodine scan in addition to Tg and ultrasound as per protocol may be required at any time during the trial for optimal management of the patient at the discretion of the clinician, but in all cases of suspected loco-regional recurrences confirmation by tissue diagnosis is required unless technically impossible. We strongly recommend that [131 I] Iodine (131-I) is **not** used for this procedure ([123 I] Iodine (123-I) is an appropriate alternative, to be administered as per local practice by sites), because:

- There is a view that an 131-I scan in the No-RAI ablation arm, even using a low dose of 185MBq might cause some degree of ablation (this is not an issue with 123-I).
- The whole body dose will be higher with 131-I (than 123-I) particularly in the No-RAI ablation arm where body retention will be longer because of the uptake in the remnant in situ. There is likely to be no or smaller remnant in the ablated arm.

10.2. Treatment of confirmed recurrence or residual disease

Sites would arrange surgery and/or RAI therapy as per local practice for patients who have a recurrence or residual disease. Treatment should be recorded on Case Report Forms. The patient should continue to be followed up.

11. Data Management and Data Handling Guidelines

Data will be collected from sites on version controlled case report forms (CRFs) designed for the trial and supplied by UCL CTC. Data must be accurately transcribed onto trial CRF's and must be verifiable from source data at site. Examples of source documents are hospital records which include patients' notes, laboratory and other clinical reports etc.

Where copies of supporting source documentation (e.g. autopsy reports, pathology reports, scan images etc.) are being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending to maintain confidentiality.

Please note that, for this trial, patients must consent to their names being supplied to UCL CTC. This is for collection of follow up information via data registries e.g. NHS Digital.

11.1. Completing Case Report Forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

All entries must be clear, legible and written in ball point pen. Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used.

The use of abbreviations and acronyms should be avoided.

Once completed the original CRFs must be sent to UCL CTC and a copy kept at site.

11.2. Missing Data

To avoid the need for unnecessary data queries CRFs must be checked at site to ensure there are no blank fields before sending to UCL CTC (unless it is specifically stated that a field may be left blank). When data is unavailable because a measure has not been taken or test not performed, enter "ND" for not done. If an item was not required at the particular time the form relates to, enter "NA" for not applicable. When data are unknown enter the value "NK" (only use if every effort has been made to obtain the data).

11.3. Timelines for data return

All sites must submit the randomisation and baseline data CRFs within 10 business days of the patient being randomised.

All other forms must be submitted within 1 month of the patient being seen.

Sites that persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subjected to

a ‘for cause’ monitoring visit. See section 14.2 (‘For Cause’ On-Site monitoring) for details.

11.4. Data Queries

Data arriving at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Data Clarification Requests will be sent to the data contact at site. Further guidance on how data contacts should respond to Data Queries can be found on the Data Clarification Request forms.

12. Pharmacovigilance

12.1. Definitions

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

Adverse Event (AE)

Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with a trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a trial treatment, whether or not related to that trial treatment. See section 12.2.1 for AE reporting procedures.

Adverse Reaction (AR)

All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between a trial treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that at any dose:

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

See section 12.2.3 for SAR reporting procedure.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

An Adverse event meeting the following criteria:

- Serious – meets one or more of the serious criteria above
- Related – assessed by the local investigator or sponsor as causally related to one or more elements of the trial treatment
- Unexpected – the event is not consistent with the applicable reference safety information (RSI)

12.2. Reporting Procedures

Adverse Event Term

An adverse event term must be provided for each adverse event. Wherever possible a valid term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 available online at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Severity Grade

The severity grade of each adverse event must be determined by using CTCAE v4.03

Causality

The relationship between the treatment and an adverse event will be assessed.

For AE's the local PI designee will assess whether the event is causally related to trial treatment.

Causal relationship to each trial treatment must be determined as follows:

- **None**
  There is no evidence of any causal relationship.
- **Unlikely**
  There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of a trial treatment). There is another reasonable explanation of the event (e.g. the patient's clinical condition, other concomitant treatments).
- **Possibly**
  There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of a trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
- **Probably**
  There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- **Definitely**
  There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

UCL CTC will consider events evaluated as related to be adverse reactions.

12.2.1. Reporting of Adverse Events (AEs)

All adverse events that occur between informed consent and the end of the trial must be recorded in the patient notes and the trial CRFs. Those meeting the definition of a Serious Adverse Reaction (SAR) that occur in patients randomised to arm 1 (RAI ablation), that are considered causally related to RAI ablation, must also be reported to UCL CTC using the trial specific SAE Report. Also refer to section 12.2.3 (Serious Adverse Reactions (SARs)).

Pre-existing conditions do not qualify as adverse events unless they worsen.

12.2.2. Overdoses

All accidental or intentional overdoses, whether or not they result in adverse events, must be recorded in the patient notes and CRFs. Overdoses resulting in an adverse reactions are classified as SARs and must be reported to UCL CTC according to SAR reporting procedures. The fact that an overdose has occurred must be clearly stated on the SAR Report. Also refer to section 12.2.3 (Serious Adverse Reactions (SARs)).

Sites must inform UCL CTC immediately when an overdose has been identified. Also refer to section 13 (Incident Reporting and Serious Breaches).

12.2.3. Reporting of Serious Adverse Reactions (SARs)

For patients randomised to receive RAI ablation (Arm 1) all SARs that occur from the signing of informed consent that are considered to be causally related to RAI ablation must be submitted to UCL CTC by fax within **24 hours** of observing or learning of the event, using the trial specific SAR Report. All sections on the SAR Report must be completed. If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAR Report to avoid unnecessary queries.

Exemptions from SAR report submission

For this trial, the following events are exempt from requiring submission on an SAR Report, but must be recorded in the relevant section of the trial CRFs:

- disease progression (including disease related deaths)
- any event occurring in patients randomised to RAI ablation (Arm1) that is not considered to be causally related to RAI ablation
- any event occurring in patients randomised to No-RAI ablation (Arm 2)

Please note that hospitalisation for elective treatment or palliative care does not qualify as an SAE.

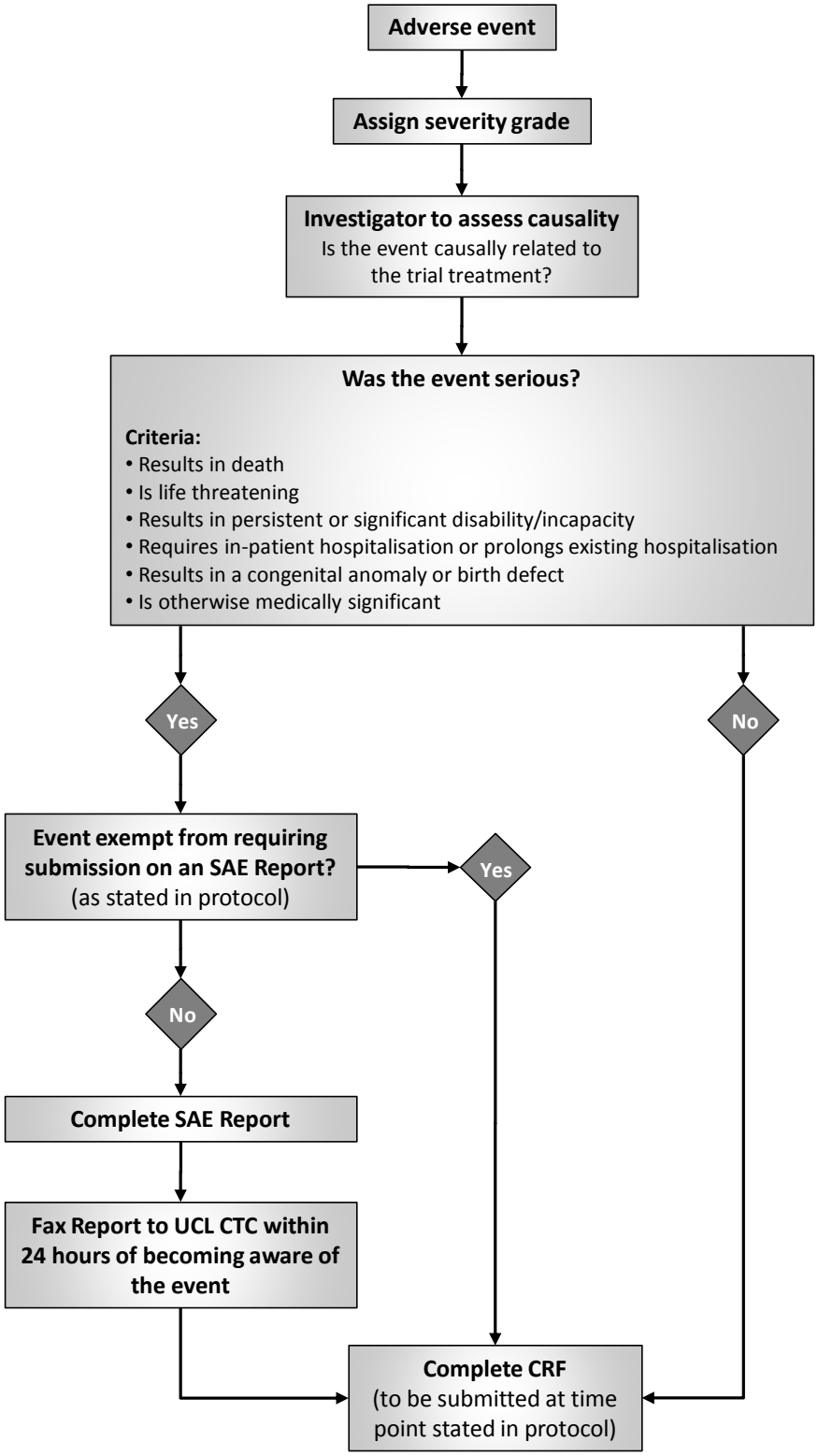
Completed SAR Reports must be faxed within 24 hours of becoming aware of the event to UCL CTC

Fax: +44 (0)20 7679 9871

SAR Follow-Up Reports

All SAR's must be followed-up until resolution and until there are no further queries. Sites must ensure any new relevant information is provided promptly. If the event term changes or a new event is added, the causality must be re-assessed by an investigator. If the event is not being reported within 24 hours to UCL CTC, the circumstances that led to this must be detailed in the SAE/SAR report to avoid unnecessary queries.

Adverse Event Reporting Flowchart (Arm 1 RAI ablation only)



SAR Processing at UCL CTC

On receipt of the SAR Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the list of expected adverse events in the approved SPC for Sodium [131 I] Iodide Capsules.

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

12.3. SUSARs

If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), UCL CTC will submit a report to the MHRA and the REC within the required timelines. Wherever possible, evaluations of causal relationship by both the site and the sponsor's clinical reviewer will be reported.

Informing Sites of SUSARs

UCL CTC will inform all PIs of any SUSARs that occur on the trial. PIs will receive a quarterly line listing which must be processed according to local requirements.

12.4. Safety Monitoring

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

Trial safety data will be monitored to identify:

- new adverse reactions to the trial treatment
- Trial-related events that are not considered related to the trial treatment regimen.

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

12.5. Pregnancy

Reporting Period

If a female patient randomised to receive RAI ablation (Arm 1) becomes pregnant within the 6 month period following ablation the site must submit a completed trial specific Pregnancy Report to UCL CTC by fax within **24 hours** of learning of its occurrence.

If a female partner of a male patient randomised to receive RAI ablation (Arm 1) becomes pregnant within the 4 month period following ablation the site must submit a completed trial specific Pregnancy Report to UCL CTC by fax within **24 hours** of learning of its occurrence.

The site must request consent from the pregnant trial patient or female partner of a male patient to report information regarding a pregnancy using:

- For female patients: the trial specific Pregnancy Monitoring Information Sheet and Informed Consent Form for trial patients
- For female partners of male patients: the trial specific Pregnancy Monitoring Information Sheet and Informed Consent Form for partners of study patients.

If consent is not given, the notification that a pregnancy has occurred will be retained by UCL CTC, however no further action will be taken on the information detailed in the report.

Exemptions from Pregnancy Report Submission

Pregnancies occurring in female patients or female partners of male patients randomised to Arm 2 (No-RAI ablation), are exempt from pregnancy report submission.

Pregnancies must be reported by faxing a completed Pregnancy Report within 24 hours of becoming aware of the pregnancy to UCL CTC
Fax: +44 (0)20 7679 9871

Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, their pregnancies must be followed-up until an outcome is determined. Follow-up Pregnancy Reports must be submitted to UCL CTC by fax within **24 hours** of learning of the outcome. Reports must include an evaluation of the possible relationship of the trial treatment to the pregnancy outcome.

SARs During Pregnancy

Any SAR occurring in a pregnant patient must be reported using the trial specific SAR Report, according to SAR reporting procedures. Refer to section 12.2.3 (Serious Adverse Reactions (SARs)) for details.

Pregnancy Report Processing at UCL CTC

UCL CTC will submit a report to the MHRA and the REC if the pregnancy outcome meets the definition of a SUSAR. Refer to section 12.3 (SUSARs) for details.

13. Incident Reporting and Serious Breaches

13.1. Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. An incident report may be requested and will be provided, but an equivalent documents (e.g. Trust Incident form) is acceptable where already completed.

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

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

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

13.2. Serious Breaches

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

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

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

Sites must have written procedures for notifying the sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches).

14. Trial Monitoring and Oversight

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

UCL CTC will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

14.1. Central Monitoring

Sites will be requested to submit screening logs and staff delegation logs to UCL CTC at the frequency detailed in the trial monitoring plan or on request and these will be checked for consistency and completeness.

Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Checks of the criteria listed on the randomisation form will be undertaken by an appropriately trained UCL CTC staff member prior to randomisation. Also refer to section 7.1 (Randomisation).

Copies of completed RAI ablation accountability logs will be collected at UCL CTC for all trial patients randomised to receive RAI ablation. Sites will be required to submit logs on request. A proportion of these will be monitored centrally to ensure completeness and correlation with data captured in the CRF. Also refer to section 8.2.5 (IMP accountability).

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File and Nuclear Medicine Site File at the frequency detailed in the trial monitoring plan. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

Data received at UCL CTC will be subject to review in accordance with section 11.4 (Data Queries).

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk, the matter will be raised urgently with site staff and escalated as appropriate (refer to sections 13 Incident Reporting and Serious Breaches and 14.2 ‘For Cause’ On-Site monitoring for further details).

14.2. ‘For Cause’ On-Site monitoring

On-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities, who will be performing the visit and when the visit is likely to occur.

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

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

14.3. Oversight Committees

14.3.1. Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and IoN trial staff from UCL CTC (see page 2). The TMG will be responsible for overseeing the trial. The group will meet regularly approximately once a year or more frequently if required and will send updates to Principal Investigators (via newsletters or at Investigator meetings) and to the NCRI Clinical Studies Group.

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

All TMG members must sign the TMG charter which outlines the TMG responsibilities for IoN.

14.3.2. Trial Steering Committee (TSC)

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

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

14.3.3. Independent Data Monitoring Committee (IDMC)

An IDMC will be formed once the trial moves to phase III.

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held annually to review interim analyses, or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

All IDMC members must sign the IDMC charter which outlines the IDMC responsibilities for IoN.

14.3.4. Role of UCL CTC

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

CTC is responsible for all duties relating to pharmacovigilance which are conducted in accordance with section 12 (Pharmacovigilance).

15. Withdrawal of patients

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

15.1. Discontinuation of Trial Treatment

A patient may be withdrawn from trial treatment whenever continued participation is no longer in the patient's best interests, but the reasons for doing so must be recorded in the patients' notes and on the relevant Case Report Form(s). Reasons for discontinuing treatment may include:

- Disease progression
- Patients withdrawing consent
- Intercurrent illness
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the site investigator's opinion

In these cases patients remain within the trial for the purposes of follow-up and data analysis according to the treatment option to which they have been allocated unless they explicitly withdraw consent.

If a patient expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used. If the patient gives a reason for their withdrawal, this should be recorded.

15.2. Future Data Collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected, and recorded on the relevant CRF. In this event data due up to the date of withdrawal must be submitted but no further data, other than essential safety date, sent to UCL CTC.

15.3. Losses to follow-up

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

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

Patients lost to follow-up may be tracked by UCL CTC via data registries e.g. NHS Digital.

16. Trial Closure

16.1. End of Trial

For regulatory purposes the end of the trial will be 11 years after the last patient has been randomised onto the trial at which point the 'declaration of end of trial' form will be submitted to the MHRA and ethics committees, as required.

Following this, UCL CTC will advise sites on the procedure for closing the trial at the site.

Once the trial has been declared, no more prospective patient data will be collected but sites must co-operate with any data queries regarding existing data to allow for analysis and publication of results.

16.2. Archiving of Trial Documentation

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

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

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

Laboratories must archive stored blood samples according to CPA and RCPath requirements.

16.3. Early discontinuation of trial

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

16.4. Withdrawal from trial participation by a site

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

17. Statistics

17.1. Sample size calculation

The IoN trial sample size comes from a non-inferiority design, with a 5-year recurrence-free rate of 95%[7] among patients who have RAI ablation (exponential parameter 0.0103). The following table shows target sample sizes for different non-inferiority margins (using nQuery), down to 87% - all with 80% power and one-sided 5% level of statistical significance, assuming 6 or 7 years accrual in total, then 3 years follow up at the end of accrual, during which most recurrences would be seen:

Allowable 5-yr rate in the no ablation group	90	89	88	87
Exponential parameter	0.0211	0.0233	0.0256	0.0279
Total number of events required	48	37	30	25
Total number of patients with 6 years accrual	606	450	354	290
Total number of patients with 7 years accrual	560	418	328	270

Our target is 560, but with a minimum of 450. With current monthly accrual rates of about 7 per month, we should reach 560 by August 2019.

However, if accrual rates decrease or the trial is stopped early, it is helpful to consider the implications of a lower sample size if we cannot reach 450. There is the possibility of allowing a non-inferiority margin of up to 7-8 percentage points (down to 87-88%) because the majority of recurrences can be treated successfully with surgery and/or high dose radioiodine therapy and are thus cured (unlike, for example, breast cancer where non-inferiority margins for therapy trials tend to be ≤5 percentage points because of the greater difficulty in treating these recurrences). Further support that a margin of >5 percentage points would be acceptable comes from some thyroid cancer clinicians (in the US and Japan) who now advocate lobectomy instead of total thyroidectomy, in which such studies show that the recurrence-free survival rate could be down to 85-87%.

[NB: we ask that each patient follow the protocol schedule of assessments for 5 years for close monitoring, but the first primary statistical analysis could be done 3 years after recruitment finishes.]

17.2. Population for analysis

The primary analyses will be intention-to-treat (ITT) and per-protocol (based only on patients who had the allocated intervention). The ITT and per-protocol analyses will be examined for consistency.

17.3. Analysis of the primary endpoint (phase III)

Disease-free survival (DFS) will be measured from the date of randomisation until the date of recurrence or death fromthyroid cancer, whichever occurs first. If patients have neither a recurrence nor die from thyroid cancer, they will be censored at the date last seen alive (or death from other causes). Because low-risk differentiated thyroid cancer

is curable in most cases, patients can live without disease for many years and so die from other causes completely unrelated to thyroid cancer. These other causes are expected to be balanced between the two trial arms, and hence potentially lead to a bias towards non-inferiority.

DFS will be compared between the two groups using a logrank test, and also a Cox regression model to allow for the stratification factors used in the randomisation. The 5-year DFS rate will be obtained for each group and the difference and 95% confidence interval estimated. If 'No-RAI ablation' is non-inferior to RAI ablation, the 5% one-sided lower limit for the difference should be no lower than -5%, is consistent with excluding a hazard ratio of 2.04 (where the expected recurrence-free rate is 95% with RAI ablation, and we allow down to 90% for non-inferiority with No-RAI ablation). The difference in rates can be obtained by (i) using the observed rates in each trial arm and (ii) by applying the observed hazard ratio to the rate in the No-RAI arm. A competing risk model can also be used to allow for deaths from other causes.

Pre-specified subgroup analyses will be based on the following factors to examine whether non-inferiority is observed in each subgroup:

- Age
- Papillary and follicular tumours
- T stage (tumour size)
- N stage
- Patients who did or did not have a prophylactic bilateral level VI dissection

17.4. Analysis of secondary endpoints (phase III)

17.4.1. Efficacy (secondary)

The time to first occurrence of loco-regional recurrence, metastatic disease or death from any cause would be compared between the two trial groups using Cox regression modelling, and the hazard ratio and 95% CI obtained. The hazard ratio will also be adjusted for the randomisation stratification factors.

The treatments, e.g. surgery and/or administered dose of RAI ablation, given for recurrence will be summarised in each group.

We will also examine the time to annual assessments from the date of the initial ultrasound scan, to check that patients in each trial group are having their clinic visits at approximately similar times (i.e. to check there is no ascertainment bias).

The Tg result from the first year will also be correlated with 5-year outcomes to see whether it can predict recurrence and mortality. If year 1 Tg is highly predictive (i.e. that a low level indicates that there are no further recurrences), the extent of follow up for future patients outside of the IoN trial could be revised.

17.4.2. Safety

Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events, version 4.03. The maximum grade per patient for each toxicity type

will be obtained, and compared between the two trial groups using a chi-squared or Fishers exact test.

As part of a long-term analysis, the time to develop a secondary tumour (incidence or mortality) will be compared using a logrank test and Cox regression model, and the hazard ratio and 95% CI obtained. Patients who do not have a secondary tumour will be censored at the date last seen alive or date of death (if not due to cancer).

17.4.3. Economic evaluation

A cost-effectiveness analysis would be part of the phase III trial. Assuming that 'No-RAI ablation' has a similar disease-free survival as RAI ablation, we will include the following costs in an economic analysis (the costs could be obtained from the larger participating sites):

- Cost of RAI ablation (and rhTSH, when used), including the number of days in hospital isolation
- Cost of re-ablation in the RAI group; and first ablation in the No-RAI group
- The cost of treating RAI induced side effects, when required
- Cost of treating a recurrence occurring within the first 5 years

Quality Adjusted Life Years (QALYs) would also be estimated using the EQ5D.

17.4.4. Health related Quality of Life

The QLQ C30 data will be scaled accordingly, and results for the 15 domains compared between the two trial groups, using a repeated measures analysis, such as mixed modelling.

18. Ethical and Regulatory Considerations

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

- the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928
- Human Rights Act 1998
- Data Protection Act 1998
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Medicines Act 1968
- Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
- Good Manufacturing Practice
- the Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

18.1. Ethical Approval

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

The trial has received a favourable opinion from the NRES Committee North East – Newcastle and North Tyneside 1.

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

18.2. Regulatory Approval

A Clinical Trial Authorisation (CTA) has been granted for the trial.

The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA.

18.3. Site Approvals

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

18.4. Protocol Amendments

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

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

18.5. Patient Confidentiality & Data Protection

Patient identifiable data, including patient name, initials, date of birth and NHS number will be required for the randomisation process and will be provided to UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at UCL.

19. Sponsorship and Indemnity

19.1. Sponsor Details

Sponsor Name:	University College London
Address:	Joint Research Office Gower Street London WC1E 6BT
Contact:	Director of Research Support
Tel:	020 3447 9995/2178 (unit admin)
Fax:	020 3447 9937

19.2. Indemnity

University College London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

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

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

20. Funding

Cancer Research UK is supporting the central coordination of the trial through UCL CTC.

21. Publication Policy

Members of the Trial Management Group will form the basis of the writing committee, and will be responsible for the first publication of the trial results. All collaborating sites will be acknowledged. Further publications based on data from the trial should be agreed by the writing committee. The clinical trials ISRCTN should be quoted on all publications.

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Appendix 1: Abbreviations

Ab	Antibody
AE	Adverse Event
AR	Adverse Reaction
ATA	American Thyroid Association
ARSAC	Administration of Radioactive Substances Advisory Committee
CCND	Central Compartment Node Dissection
CI	Chief Investigator
CPA	Clinical Pathology Accreditation UK Ltd
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CTSA	Clinical Trial Site Agreement
CVA	Cerebrovascular accident/ Stroke
DTC	Differentiated Thyroid Cancer
DPA	Data Protection Act
EudraCT	European Clinical Trials Database
FNAC	Fine-needle aspiration cytology
GBq	Gigabecquerel (1000 Mbq)
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IRMER	Ionising Radiation Medical Exposures Regulations
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-treat
MBq	Megabecquerel (37 Mci, 1000000 Becquerel)
mCi	Millicurie
MDT	Multi-Disciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
NCI	United States National Cancer Institute
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NED	No clinical Evidence of Disease
NHS	National Health Service
NIMP	Non-Investigational Medicinal Product
NRES	National Research Ethics Service
PI	Principal Investigator
PTC	Papillary Thyroid Cancer
QALY	Quality Adjusted Life Year
RAI	Radioactive Iodine
RCPath	Royal College of Pathologists
REC	Research Ethics Committee
rhTSH	Recombinant human Thyroid Stimulating Hormone
RLN	Recurrent Laryngeal Nerve
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
Tg	Thyroglobulin
TMF	Trial Master File

TMG	Trial Management Group
TNM	TNM (Tumour, lymph Node, Metastasis) classification system
TSC	Trial Steering Committee
TSH	Thyroid stimulating hormone
T3	Triiodothyronine/liothyronine
T4	Tetraiodothyronine/levothyroxine/l-thyroxine
TT	Total Thyroidectomy
UCL CTC	CR UK and UCL Cancer Trials Centre
UK	United Kingdom
US	Ultrasound
WCBP	Women of child bearing potential

Appendix 2: Schedule of Assessments

	Pre-trial	Consent	Randomisation	Initial neck US (All patients)	Initial Stimulated Tg	Ablation (arm 1 patients only)		2 Months after initial stimulated Tg		6-9 months after initial stimulated Tg
Total Thyroidectomy	X									
Histological confirmation	X									
Baseline bloods and thyroid function tests	X									
Negative pregnancy test		X				X				
Medical history		X								
Clinical Exam & AE assessment	X							X		X
Call UCL CTC to randomise patient			X							
Send histology slides for central review			X							
Radioactive Iodine (RAI) ablation, Sodium (131 I) iodide at 1.1GBq						X				
Neck Ultrasound				X[1]						X
Quality of Life questionnaires: QLQ-C30, QLQ-H&N35 and E5-QD		X			X[2]			X		X[4]
TSH, Tg Ab and Tg assay, Free T3, Free T4 (local bloods)					X[3]			X		X

[1]Not within 8 weeks post surgery, must be before ablation (arm 1).
[2]QoL preferable to be given to patient before stimulated Tg and definitely before ablation
[3]Post hormone withdrawal or rhTSH administration as per protocol, samples can be taken on day 4 or 5 if rhTSH given.
[4]For patients on rhTSH local bloods to be taken on Day 1 prior to rhTSH administration

	Follow up visits (commence 6 months after the 6-9 month visit)									
	6 month	**12 month**	**18 month**	**24 month**	**30 month**	**36 month**	**42 month**	**48 month**	**54 month**	**60 month**
Clinical Exam & AE assessments	X	X	X	X	X	X	X	X	X	X
Neck ultrasound	X	X		X		X		X		X
Quality of Life questionnaires: QLQ-C30, QLQ-H&B35 and E5-QD	X	X	X	X	X	X	X	X	X	X
TSH, Tg Ab and Tf assay, free T3, Free T4 (local bloods)	X	X	X	X	X	X	X	X	X	X

Appendix 3: Protocol Version History

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
1.0	30/06/2011	Original submission	n/a	n/a
2.0	18/08/2011	N/A unapproved	Title Page 3.1.1 4.0 11.6 17.1 17.2 17.4	Addition of clinicaltrials.gov reference and CTA no Change so all investigators must be medical doctors Change so informed consent process must be documented in patients notes and update to site staff responsibilities Section on periodic safety reports removed so in line with new safety reporting Amendment to REC name Removal of Type A text as a CTA will now be received for IoN following MHRA confirmation Change to amendment text so in line with CSP process
3.0	15/09/2011	N/A unapproved	1.1 and 5.5.2 3.2.1	Exclusion criteria added Change so ARSAC research certificate is only required where applicable
4.0	07/10/2011	Amendment 1 Substantial	Title Page 8.6 18.1	Addition of CTA number Update to Histological review so samples are sent to UCL CTC Change in sponsor details
4.1	22/11/2011	N/A Non substantial	TMG update 1.1 and 5.5.2 4.0 6.1 7.0 8.3 8.5 9.0 Various sections	Removal of Sue Clarke and addition of Valerie Lewington Correction to eligibility criteria to clarify Follicular/ Hürthle cell cancer greater than 4 cm (rather than 2cm) is ineligible Removal of patient diary from protocol text as this is not applicable Confirmation of randomisation changed from ‘fax’ to ‘email’ Addition of NIMPs Sodium [131 I] Iodide (140- 185 MBq), Sodium [123 I] Iodide, Technetium 99m pertechnetate Ultrasound can be undertaken with Technetium scan if deemed necessary Details of long term follow-up CRF added Text added detailing Tg doubling time Clarification of IMP as Sodium [131 I] Iodide

5.0	05/07/2012	Amendment 4 - Urgent Safety Measure	see sections 1.0, 6.1, 8.3, 8.4, 8.7, 16.4	Urgent Safety Measure to remove Technetium scan and RAI scan at 6-9 months throughout protocol and replace with neck ultrasound.
			Contact details	UCL CTC contact phone number and trial email changed
			TMG members	Addition of Steve Turner, David Richardson and Dymphna Lee, removal of Nick Reed and Colin Lunt
			4.0	Amended wording to allow flexibility on timelines for giving PIS and taking consent
			5.0	Clarification of wording, removed reference to hemithyroidectomy
			5.3	Removal of FBC and Biochemistry
			5.5.3	Clarified reporting timeframe for pregnancies and contraception measures
			5.5	Inclusion criteria added – histological material available for review
				Exclusion criteria for pregnant/lactating patients clarified
				Added reference to Arm 1 and Arm 2
			6.0	Added pregnancy test, Adverse Events to assessments
			8.3 & 8.4	Section moved to new section 21
			8.6	Translational Research
			9.1	Clarification of isotope use in detection of recurrence of disease
			11.0	Reporting procedures revised SAEs collected for Arm 1 only, reporting timeframes updated due to urgent safety measure
			12.0	Updated UCL CTC standard wording, clarified IDMC will be formed for Phase III
			18.1	Sponsor contact details updated
			22.0	References updated
			8.8	Summary schedule updated to match assessments
			Various sections	Minor formatting changes, corrections of typographical errors and updates to protocol template wording throughout protocol

6.0	22/05/2013	Amendment 8 Substantial	1.0 1.2 2.1 2.2.3 4.0 5.3 & 8.1 5.5.1, 5.5.2 6.0 7.2 8.0 8.6 8.7 9.0 10.5 11.0 18.0 21.0 Appx 1 Various sections	Trial summary updated Trial schema updated Minor changes to wording Trial objectives clarified Clarification of informed consent process for patients with language difficulties Informed consent timelines modified from 7 days to 14 days prior to randomisation Inclusion/Exclusion criteria clarified. Papillary Thyroid Cancer pT3 now includes minimal extrathyroidal extension, multifocal tumours (including multifocal microcarcinoma explained. Stratification updated to include T1a(m) Clarification to hormone withdrawal TSH suppression guidance Order of assessments clarified for Arm 1 and Arm 2, and for patients receiving rhTSH or hormone withdrawal Translational research section moved from section 21.0. Summary of assessments table updated and reformatted Clarification on investigations to use where recurrent/residual disease is suspected. Data query procedure updated Pharmacovigilance reporting procedure modified, only Serious Adverse Reactions (SARs) to be collected. Clerical change to sponsor contact details References updated Abbreviations list updated Minor formatting changes, corrections of typographical errors and updates to new protocol template wording throughout protocol.
6.1	05/07/2013	Amendment 9 Non-substantial	8.0	Correction to formatting of header in section 8.3 Assessments during treatment, renumbering of 8.3 to 8.7 inclusive. Removal of duplicated text on page 35. Table of contents updated.

7.0	29/10/2015	Amendment 22 Substantial	TMG Members 1.0 5.5.1 & 5.5.2 8.4 16.1 Various sections	Beng Yap and Dymphna Lee removed, Paul Patterson and Steve Davis added Trial Summary updated Inclusion/Exclusion criteria updated following BTA 2014 guidelines and altered definition of 'low risk DTC' Order of assessments at 6-9 month visit clarified Sample size calculation corrected Minor formatting changes, corrections of typographical errors and updates to protocol template wording throughout protocol
8	16/05/2018	Amendment 34 Substantial	1.0 1.2 6.4 9.8 & various sections 17	Correction made to Trial Summary following Inclusion/Exclusion criteria update Trial Schema corrected following sample size update Inclusion/Exclusion criteria updated to include both TNM7 and TNM8 Inclusion/Exclusion criteria format updated. Criteria for pT1a clarified Removal of collection of blood samples for translational research Additional information added following correction of sample size calculation
9	17/07/2018	Amendment 36	6.4	Correction made to exclusion criteria for TNM8