A Randomized Controlled Clinical Trial on the Effectiveness of Lithium in comparison to Carbimazole as a Bridging Therapy prior to Radioactive Iodine for Hyperthyroidism

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CONTENT

LIST OF ABBREVIATIONS

<List commonly used abbreviations/acronyms>

<RAI>	<Radioactive Iodine>
<RP>	<Renal Profile>
<LFT>	<Liver Function Test>
<TFT>	<Thyroid Function Test>
<ATD>	<Antithyroid Drug>
<CMZ>	<Carbimazole>
<TED>	<Thyroid Eye Disease>
<SAE>	<Serious Adverse Events>
<AE>	<Adverse Events>

RESEARCH SYNOPSIS

Study Title	A randomized controlled trial on the effectiveness of lithium in comparison to carbimazole as a bridging therapy prior to radioactive iodine for hyperthyroidism.
Objective	Primary To assess the proportion of cure at 6months of radioactive iodine between those who were pre-treated with lithium versus carbimazole. Secondary To assess change in serum thyroid hormone levels following two months of lithium versus carbimazole therapy prior to the administration of radioactive iodine.
Study Designs	A prospective randomized controlled, open label, single centre study. Subjects will be randomized into lithium or carbimazole arms in a 1:1 ratio. Lithium arm will receive tab Lithium Carbonate 300mg OD while Carbimazole arm will receive tab Carbimazole 10mg OD for a duration of two months prior to radioactive iodine treatment.
Study Endpoints / Outcomes	Changes in the thyroid hormone levels at 2 months of treatment and at months 1,3 and 6 following radioactive iodine.
Study Population	All adult patients who are 18 years and above with hyperthyroidism either newly diagnosed or relapse disease secondary to Graves' Disease, toxic multinodular goitre and toxic adenoma who are planned for radioactive iodine therapy as a definitive treatment from 18/12/2020 till 31/12/2021 at Pusat Perubatan Universiti Kebangsaan Malaysia.

Inclusion / Exclusion Criteria	Inclusion Criteria
	• Adult patients aged 18 years old and above with thyrotoxicosis who have been planned for definitive RAI:
	  o consented for radioactive therapy as a definitive treatment.
	  o able to comply with requirement of radioiodine therapy.
	  o FT4 level below 40pmol/L.
	
	Exclusion Criteria
	• Pregnancy or Lactating mother
	• Moderate to severe and active thyroid eye disease based on EUGOGO criteria, requires steroid cover
	• Renal impairment, egfr <45ml/min (stage 3b)
	• Underlying active malignancy
	• Underlying active schizophrenia or bipolar disorder
	• Patients on medications that may interact with lithium (refer to **APPENDIX 1**)
	• Patients on medications that may interfere with RAI effectiveness:
	  o Amiodarone
	  o Less than a month of intravenous contrast medium
	• Previous RAI < 6months
	• Previous history of adverse effect following exposure to lithium or carbimazole.
	• Thyroid carcinoma

Sample Size	86 subjects
Study Duration	18/12/2020 – 31/12/2021

BACKGROUND AND SIGNIFICANCE

Hyperthyroidism is a state of overactive thyroid gland due to autoimmune Graves' Disease, toxic multinodular goitre or toxic adenoma. Radioactive iodine (RAI) therapy is a common treatment modality for hyperthyroidism either as primary treatment or after failure of medical treatment. The aim of radioactive iodine therapy is a stable restoration to euthyroid state, however, a substantial proportion of patients become hypothyroid.

Although generally safe, radioiodine therapy has some potential side effects include gastrointestinal symptoms, radiation thyroiditis, sialadenitis/xerostomia, bone marrow suppression, gonadal damage and pulmonary fibrosis. Therefore it is pivotal to render cure in patients who are undergoing radioactive iodine at the first attempt to minimize the unwanted adverse effects.

Cure rate within a year post RAI is around 72%, however cure rates seems to differ from centre to centre. Several factors have been found to affect the success of RAI therapy and some of the known ones are prior use of thionamide, hyperthyroid state, gender, dose of RAI, RAI uptake and retention of RAI in the thyroid gland.

Simultaneous use of antithyroid drug (ATD) with RAI has consistently been shown to result in lower efficacy and higher failure rate than treatment with RAI alone.[1-5] Antithyroid drug have a radioprotective effect and pre-treatment with ATD has been shown to increase the risk of treatment failure with subsequent RAI. The result is consistent even if the drugs are discontinued 4-7 days before RAI therapy. Carbimazole (CMZ) is the current standard therapy in the management of hyperthyroidism prior to radioactive iodine therapy. Connell *et al.*, reported that CMZ stopped 5 days before RAI reduced the rate of hypothyroidism at 1-year compared to non-pretreated patients.[6] There are two other studies that have reported CMZ pre-treatment reduced the efficacy of RAI therapy.[7,8] In a meta-analysis of 14 randomized controlled trials, adjunctive ATD, including CMZ, was associated with an increased risk of treatment failure with RAI.[9] Despite these evidences, ATD are still being given in clinical practice prior to RAI in an attempt to avoid thyroid storm associated with high levels of thyroid hormones prior to RAI administration.

It is important to note that since Malaysia do not produce its own RAI and has to imported from overseas there will always be a significant waiting period. The waiting period may range between 2-3months in most of the centres including in Pusat Perubatan Universiti Kebangsaan Malaysia. In the past, patients would be continued on the usual ATD until 3days before the administration of RAI. Unfortunately, the ongoing use of ATD continued until prior to RAI may result in lowering of the RAI uptake and thus reduce the efficacy of RAI therapy. This is where an alternative bridging therapy with lithium may offer a better alternative especially in terms of RAI uptake.

Lithium has been shown not to interfere with the RAI uptake. In fact, some studies demonstrated lithium improves the success rate of RAI.[10,11] Lithium plays multiple roles in thyroid hormone synthesis process. Lithium inhibits the coupling of iodotyrosine residues to form iodothyronines thyroxine (T4) and triiodothyronine (T3), and inhibits release of T4 and T3.[12] Lithium blocks the release of organic iodine from the thyroid gland, therefore it is able to increase RAI retention in the thyroid and does not interfere with thyroidal RAI uptake.[13]

Lithium use in treating hyperthyroidism has not been used widely due to its potential adverse effects including a spectrum of central nervous system, cardiovascular, and renal side effects namely confusion, coma, seizures, ventricular irritability, sinus node dysfunction, sinoatrial block, nephrogenic diabetes insipidus and electrolyte imbalance. However these adverse effects associated with higher doses of lithium. In this particular study a very low dose of lithium (300mg daily) will be used. Previous studies showed that the occurrence of significant side effects of lithium was low with lower doses. The study by Bal et al used a dose of 300mg three times daily for 21 days did not demonstrate any severe adverse effects and only a small group of patients experienced mild gastrointestinal symptoms.

Currently hyperthyroidism is mainly being treated with medical therapy using carbimazole for a duration of 12 to 18 months duration. However, the relapse rate can be as high as 80% following cessation of ATD due to the nature of the disease. Hence, some patients will need RAI as a definitive treatment because it is a well-known fact that another course of ATD in this kind of patients will not render cure. In certain patients, eg those with thyrotoxic cardiomyopathy or hypokalaemic periodic paralysis RAI would be a primary treatment because it is important to render cure in these subset of patients to avoid cardiovascular sequeale.

In view of the waiting period to receive RAI, most patients will be pre-treated with ATD prior to RAI. However, some patients may develop side effects towards carbimazole such as liver impairment, allergic reaction or agranulocytosis. In this respect, lithium is being used as an alternative treatment. To the best of our knowledge there are no head to head study comparing lithium versus carbimazole as the pre-treatment medications prior to RAI. This would be the first study to explore the effects of the two medications prior to RAI and the novelty of this study would shed some insights into their roles and clinical applicability as well as filling up the gaps of the current literature.

HYPOTHESES

In relation to the overall objective, the following are the hypotheses:

- Lithium resulted in higher proportion of cure compared to carbimazole at 6 months of radioactive iodine.
- Lithium resulted in comparable thyroid hormone levels as carbimazole at two months following treatment prior to RAI administration.

OBJECTIVES

Primary

To assess the proportion of cure at 6 months of radioactive iodine between those who were pre-treated with lithium versus carbimazole.

Secondary

To assess change in serum thyroid hormone levels following two months of lithium versus carbimazole therapy prior to the administration of radioactive iodine.

METHODOLOGY

Study Design

This is a prospective randomized, open label, single center interventional study comparing the effectiveness of lithium versus carbimazole in lowering the thyroid hormone levels in patients undergoing radioactive iodine.

Patients will be randomized into lithium or carbimazole arms in a 1:1 ratio. Patients will receive either lithium carbonate 300mg once daily or carbimazole 10mg once daily, which is the current standard therapy. The necessary precautions will be given with regards to the study drugs. Patients will be on the above treatment for a duration of 2 months and carbimazole will be stopped 3 days prior to radioactive iodine treatment whereas lithium will be discontinued on day 3 post RAI as per usual practice. RAI will be administered at a fixed dose of 15mCi in both groups.

Antithyroid drug (ie. Methimazole or carbimazole) is restarted if needed (in symptomatic patients with FT4 of more than 40 pmol/L) at least a week after radioactive iodine and titrated as per standard treatment protocol.

Patients are declared to be cured at the end of 6 months based on thyroid function test and requirement of treatment either with thyroxine or antithyroid drug.

Randomization

Block randomization method will be utilised to randomize subjects into the two groups by selecting treatment arm from a box consisting of 8 options (4 lithium and 4 carbimazole). Once the box is empty, it will replenished by the same 8 options.

Assays and values

Thyroid Function Test
Thyroid Stimulating Hormone (TSH) and Free T4 (FT4) are measured using Chemiluminescent Microparticle Immunoassay (CMIA) method.
The normal range for TSH is 0.35-4.94 uIU/ml and for FT4 is 9-19.05 pmol/L.

Renal Profile
Renal profile is measured by Indirect Ion selective electrode (ISE) method, and urea and creatinine are measured using urease and Jaffe's method respectively.
The normal range for creatinine is 50.4-98.1 umol/L.

eGFR
eGFR is calculated using MDRD formula: $186 \times (\text{creatinine}/88.4)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$

Lithium Therapeutic Drug monitoring
Lithium level measured using Colorimetric method. Target serum concentration ranges from 0.6-1.2mM. Serum level >1.5mM is associated with sharp increase in severe adverse effects.

Definition of cure
Cure is defined as achievement of euthyroidism or hypothyroidism at 6 months after radioactive iodine therapy. Euthyroidism is defined as having serum TSH and Free T4 level within normal range without anti thyroid drug. Hypothyroidism is defined as having elevated TSH with low or normal free T4 level or requiring thyroxine replacement.

Setting

Patients who are able to comply with the requirement of radioiodine therapy and consented to participate in this trial will be given appropriate counselling. These patients will be screened for inclusion and exclusion criteria. A written informed consent will be obtained and patients will then be recruited into this study.

Once recruited, history, physical examination including baseline eye examination for possible Thyroid Eye Disease (TED) will be carried out. *TED* as defined according to the presence of eye signs in categories 2–6 of the NOSPECS classification and determined clinical activity score of thyroid eye disease according to EUGOGO criteria.

Patients will be then assessed for baseline thyroid function test (TFT), renal profile (RP) and liver function test (LFT) during screening. Patients will receive either lithium carbonate 300mg once daily or carbimazole 10mg once daily, which is the current standard therapy. The necessary precautions will be given with regards to the study drugs.

Patients will be enquired of any possible side effects during the clinic visits. Lithium levels will be checked at week 1 and at the end of 2 months of initiation (refer study flow chart). If patient develops intolerable side effects or the lithium level exceeded therapeutic range, the confounding drug will be stopped and patient will be managed accordingly. The patient will subsequently be withdrawn from the study. It is important to note that the lithium dose used in this study is of low dose, hence the side effects risks anticipated would be low.

Current waiting period in PPUKM is about 2months. Patients will be on the above treatment for a duration of 2 months and carbimazole will be stopped 3 days prior to radioactive iodine treatment. RAI will be administered at a fixed dose of 15mCi in both groups. Bloods will be drawn for TFT, RP, LFT and lithium level on the RAI day. Lithium will be discontinued on day 3 post RAI. The timeline for stopping both the carbimazole and lithium are as per clinical practice guidelines. Patients will be followed up at months 1, 3 and 6 post RAI with TFT during each visit.

Study Population

All adult patients who are 18 years and above with hyperthyroidism either newly diagnosed or relapse disease secondary to Graves' Disease, toxic multinodular goitre and toxic adenoma who are planned for radioactive iodine therapy as a definitive treatment will be included in this study.

The study period is from 18/12/2020 till 31/12/2021 at Pusat Perubatan Universiti Kebangsaan Malaysia.

Inclusion Criteria

- Adult patients aged 18 years old and above with thyrotoxicosis who have been planned for definitive RAI:
    - consented for radioactive therapy as a definitive treatment.
    - able to comply with requirement of radioiodine therapy.
    - FT4 level below 40pmol/L

Exclusion Criteria

- Pregnancy or Lactating mother
- Moderate to severe and active thyroid eye disease based on EUGOGO criteria, requires steroid cover
- Renal impairment, egfr <45ml/min (stage 3b)
- Underlying active malignancy
- Patients on medications that may interact with lithium (refer to **APPENDIX 1**)
- Patients on medications that may interfere with RAI effectiveness:
    - Amiodarone
    - Less than a month intravenous contrast
- Previous RAI < 6months
- Previous history of adverse effect following exposure to lithium or carbimazole.
- Thyroid carcinoma

Refusals, withdrawals, lost to follow-up

Patients can withdraw themselves from the study at any point of time. If patient had changed the decision and opted out of radioactive iodine, endocrinologist should be contacted immediately and clinic visits will be arranged to review the patient. If patients were lost to follow-up, weekly phone calls will be made on 4 consecutive weeks. Patients may be withdrawn if the investigator deems that it is detrimental or risky for the patient to continue. Follow up visits at endocrine clinic will be arranged for all withdrawn patients. Withdrawn subjects will not be replaced

Adverse Events

Definition:

Adverse event (AE)
Any untoward medical occurrence in a subject administered an investigational intervention and which does not necessarily have a causal relationship with treatment.

An AE includes:

- A clinically significant worsening of a concomitant illness
- A clinical laboratory adverse event: a clinical laboratory abnormality which is clinically significant, i.e an abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management, Active management includes active treatment or further investigations, for example change of medicine dose or more frequent follow-up due to the abnormality.

In this trial, the following should be reported as AE:

- Treatment emergent symptoms which include:
    - Medical conditions or signs or symptoms that was absent before starting study treatment.
    - Medical conditions or signs or symptoms present before starting study treatment and worsen (increase severity or frequency) after starting study treatment.
- Abnormal laboratory values or tests that induce clinical signs or symptoms or require therapy.
- Any adverse experience even if no drug has been administered, for example during run in or wash out phase of the study.
- Any doubtful event should be treated as an AE.

Unexpected adverse event
Any adverse event not reported in the safety section of the Investigator's Brochure or if the event is of greater frequency, specificity or severity.

Serious adverse event (SAE)
Any adverse event occurring that:

- Results in death
- Is a life threatening adverse experience defined as any adverse event that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. Note that this does not include a reaction that had it occurred in a more severe form, it would have caused death.
- Results in subject hospitalisation or prolongation of existing hospitalisation.

The following hospitalisations are not considered to be SAEs:

- Those planned before entry into the study.
- Elective treatment for a condition unrelated to study indication or study treatment
- Occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria in SAE definition)
- Part of normal treatment or monitoring of the study indication and are not associated with any deterioration in condition.
- Results in a significant or persistent disability or incapacity defined as any event that results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.
- Is any instance of overdose, either accidental or intentional (suspected or confirmed)
- Is any other important medical event, based upon appropriate medical judgement, that may jeopardise the subject or may require medical or surgical intervention to prevent or avert one of the outcomes listed above.

Detecting and documenting AE

- Information about all AEs, whether volunteered by the patient, discovered by investigator questioning or detected through physical examination, laboratory test or other means, would be documented on the Adverse Event Form and followed up as appropriate. The AE form should be emailed to the coordinating investigator Dr. Deviga a/p Lachumanan at devigaonline@gmail.com.

- When eliciting experiences of AE from a subject, ask a standard non-leading question like "Do you feel different in any way since starting the new treatment/the last visit?" This question will be put to the subject in his/her own language at each study visit.

- Each AE should be described by:
  Nature of AE
    - This should be documented in terms of a medical diagnosis(es). When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject.

  Duration:
    - Start and end dates

  Assessment of causality:
  The investigator should attempt to explain each AE and assess its relationship, if any, to the study treatment. Causality should be assessed using the following definitions:
    - Very likely
      - The AE follows a reasonable temporal sequence from study treatment administration
      - Abates upon discontinuation of study treatment
      - Reappears on repeated exposure (re-challenge)
    - Probable
      - The AE follows a reasonable temporal sequence from study treatment administration
      - Abates upon discontinuation of study treatment
      - Cannot reasonably be explained by known characteristics of the subject's clinical state
    - Possible
      - The AE follows a reasonable temporal sequence from study treatment administration.
      - But could have been produced by the subject's clinical state or other mode of therapy administered to the subject
    - Doubtful
      - The temporal association between study treatment and AE is such that the study treatment is not likely to have any reasonable association with the observed event
    - Very unlikely
      - The AE is definitely produced by the subject's clinical state or other mode of therapy administered to the subject

  The degree of certainty with which an AE is attributed to study treatment or alternative cause like natural history of disease or concomitant treatment should be guided by the following considerations:
    - Time relationship between treatment and occurrence of AE
    - De-challenge and re-challenge information, if applicable
    - Known pharmacology of the drug
    - Dose response relationships
    - Lack of alternative explanations i.e. no concomitant drug used and no other inter-current disease
    - Reaction of similar nature being previously observed with this drug or class of drug
    - Reaction having often been reported in literature for similar drug

Severity of AE

- Mild: awareness of signs or symptoms, but they are easily tolerated
- Moderate: enough discomfort to cause interference with usual activity
- Severe: incapacitating, with inability to work or do usual activity.

Note that a severe AE is not necessarily serious. The term severe is a measure of the intensity while a serious AE is determined based on regulatory criteria. A life threatening AE is an SAE.

Final outcome

- Recovered/ resolved - The subject has fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first trial-related activity after the subject signed the informed consent
- Recovering/resolving - The condition is improving and the subject is expected to recover from the event. This term is only applicable if the subject has completed the trial or has died from another AE.
- Recovered/ resolved with sequelae - The subject has recovered from the condition, but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as SAE.
- Not recovered/not resolved - The condition of the subject has not improved and the symptoms are unchanged, or the outcome is not known.
- Fatal - This term is only applicable if the subject died from a condition related to the reported AE.
- Unknown - This term is only applicable if the subject is lost to follow-up

Reporting SAE

- Information about all SAE will be documented in the AE form and reported to Coordinating Investigator of the study, Dr. Deviga a/p Lachumanan at devigaonline@gmail.com and UKM ethics directly within 24 hours.

Treatment and follow up of AE

- Treatment of any AE is at the sole discretion of the investigator who should follow up subjects with AE until the event has resolved or until the condition has stabilised. Otherwise appropriate medical care should be arranged for the patient. Abnormal tests should be repeated until they return to baseline levels or an adequate explanation of the abnormality has been found.
- Adverse events will be explored and documented at each clinic visit.

Safety update

- Any safety updates will be notified to UKM ethics committee.

Sample size

Sample size calculation was calculated using two population proportion formulae. Prior data indicate that the proportion of cure of the patients receiving lithium was 0.91 (Bogazzi et al.)[1] and the proportion of cure of the patients receiving carbimazole was 0.57 (Kartamihardja et al.)[2] Thus a minimum sample size of 34 samples per group to be able to reject null hypothesis with probability power of 0.9. The type 1 error probability associated with this test of the null hypothesis is 0.95. Person's Chi Square test for independence will be used to evaluate this null hypothesis. With additional of two 20% dropout rate, the sample size is 43 samples per group.

Hypothesis (Equality)

$H_0: p_1 = p_2$

$H_a: p_1 \neq p_2$

Formulae for Sample Size Calculations

Sample size (n) :

$$= \frac{\left\{Z_{1-\frac{\alpha}{2}}\sqrt{2\bar{p}(1-\bar{p})} + Z_{1-\beta}\sqrt{p_1(1-p_1)+p_2(1-p_2)}\right\}^2}{(p_1-p_2)^2}$$

where n = sample size, Z = level of confidence, α = alpha, β = beta, p_1 = proportion in Group 1, and p_2 = proportion in Group 2.

$$= \frac{\left\{Z_{1-\frac{0.05}{2}}\sqrt{2(0.740)(1-0.740)} + Z_{1-0.10}\sqrt{0.910(1-0.910)+0.570(1-0.570)}\right\}^2}{(0.910-0.570)^2}$$

$$= \frac{\left\{1.96\sqrt{0.385} + 1.29\sqrt{0.327}\right\}^2}{(0.340)^2}$$

$$\approx \mathbf{34\ samples}$$

Reference:

1. Bogazzi F, Giovannetti C, Fessehatsion R et al. Impact of lithium on efficacy of radioactive iodine therapy for Graves' disease: a cohort study on cure rate, time to cure, and frequency of increased serum thyroxine after antithyroid drug withdrawal. *J Clin Endocrinol Metab.* 2010 Jan;95(1):201-8.
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Study Duration and Timeline

Stage 1:
Recruitment period is 12 months; commencing from the dates of ethics approval. There are 2 phases of this study:

- Phase 1: Patients will be followed up for 2months duration from recruitment till date of RAI.
- Phase 2: Patients will be followed up at 1, 3, and 6months post RAI therapy.

Stage 2:
Data collection and Data Analysis will cover a period of 18months, from January 2021 till Jun 2022.

Stage 3:
Presentation and publication will take about 6months period from March till September 2022.

The participation duration of each subject is 8months in total. (Refer to Appendix 2)

Study Visits and Procedures

Time line	Carbimazole arm	Lithium arm
0 (recruitment)	History, physical examination including baseline eye examination for possible thyroid eye disease will be carried out. 10mls blood will be drawn for baseline TFT, RP) and LFT.	
1week later	-	Patients will be inquired of any possible side effects. 4mls blood will be drawn for lithium level and RP
2 months later (on RAI day)	History and Physical Examination and 8mls of blood drawn for TFT, RP, LFT	History and Physical Examination and 10mls of blood drawn for TFT, RP, LFT and TDM lithium. Patients will be inquired of any possible side effects.
1 months after RAI	History and Physical Examination and 2mls of blood drawn for TFT	
3 months after RAI	History and Physical Examination and 2mls of blood drawn for TFT	
6 months after RAI	History and Physical Examination and 2mls of blood drawn for TFT	

Statistical Analysis Plan

Data will be entered and analysed using SPSS version 23 with appropriate statistical tools. Normally distributed data will be presented as mean±SD. Non-normally distributed data will be presented as median and interquartile range. For comparison of baseline characteristics between the two groups, (lithium vs carbimazole) the independent sample t-test will be used if the numerical data is normally distributed and the Mann-Whitney U-test for non-normally distributed data. Pearson's Chi-square test will be used to compare the categorical data between the two groups (lithium vs carbimazole). $P < 0.05$ will be used to determine statistical significance; data reported as mean Standard Deviation.

Risk and Benefit to Participants

Risks:

Lithium has been used extensively for treatment of various medical conditions. The dose used for this study is much lower. The study procedures are all routine procedures for the disease/condition studied. There is thus minimal risk for subjects.

Benefits:

This study may benefit you by reducing your high thyroid hormone level in your body prior to undergoing radioactive iodine therapy without compromising the outcome of the radioactive iodine treatment.

Risk Benefit Assessment

There is minimal risk for this study as the treatment of these patients are in accordance to standards of care. Study findings shall potentially greatly improve treatment outcomes. The expected benefit outweighs the risk to the participants and thus this study should be supported. This study examines patient-outcomes and results will be beneficial for policy makers to plan and structure comprehensive care and tailor it to best suit the patients. If patient develops intolerable side effects or lithium level above therapeutic range, the confounding drug will be stopped and will be managed accordingly. The patient will be excluded from this study.

Ethics of Study

This study will be conducted in compliance with ethical principle in the Declaration of Helsinki and Malaysian Good Clinical Practice Guidelines.

Informed Consent

Patients shall be informed of the study during their usual clinic visits. They will be requested to contact investigators if they are interested. An appointment will be made where the patient information sheet will be provided and explained to them. If they are willing to participate, the consent forms will be signed and dated. If they need to, they are allowed to take the information sheet home to consult with their family members, and another day for getting consent arranged.

Privacy and Confidentiality

Study subjects' personal details will be remained confidential. Study ID will be assigned to each subject and the data that are transcribed into standardized data entry forms will only contain the study ID. All data will be entered into computer that is password protected. After completion of the study, the data saved into the computer will be erased. The hardcopy and pen drive of the data will be stored in a locked cabinet of the principle investigator and maintained for a minimum of 7 years after the completion of the study. Both will then be destroyed after 7 years of storage. Subjects will not be allowed to view their personal study data, as the data will be consolidated into a database. Subjects can write to the investigators to request access to study findings.

Conflict of Interest

The investigators declare they have no conflict of interest.

Publication Policy

No personal information will be disclosed, and subjects will not be identified when the findings of the survey are published.

Termination of Study

If the study needs to be terminated, participants will be informed, and follow-up visits will be arranged.

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12. N. Bagchi, T. R. Brown, and R. E. Mack, "Studies on the mechanism of inhibition of thyroid function by lithium," *Biochimica et Biophysica Acta*, vol. 542, no. 1, pp. 163–169, 1978.

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Appendix 1

LIST OF MEDICATIONS NOT PERMITTED DURING THIS TRIAL

During this trial, subjects participating in this research cannot be on these medications concomitantly:

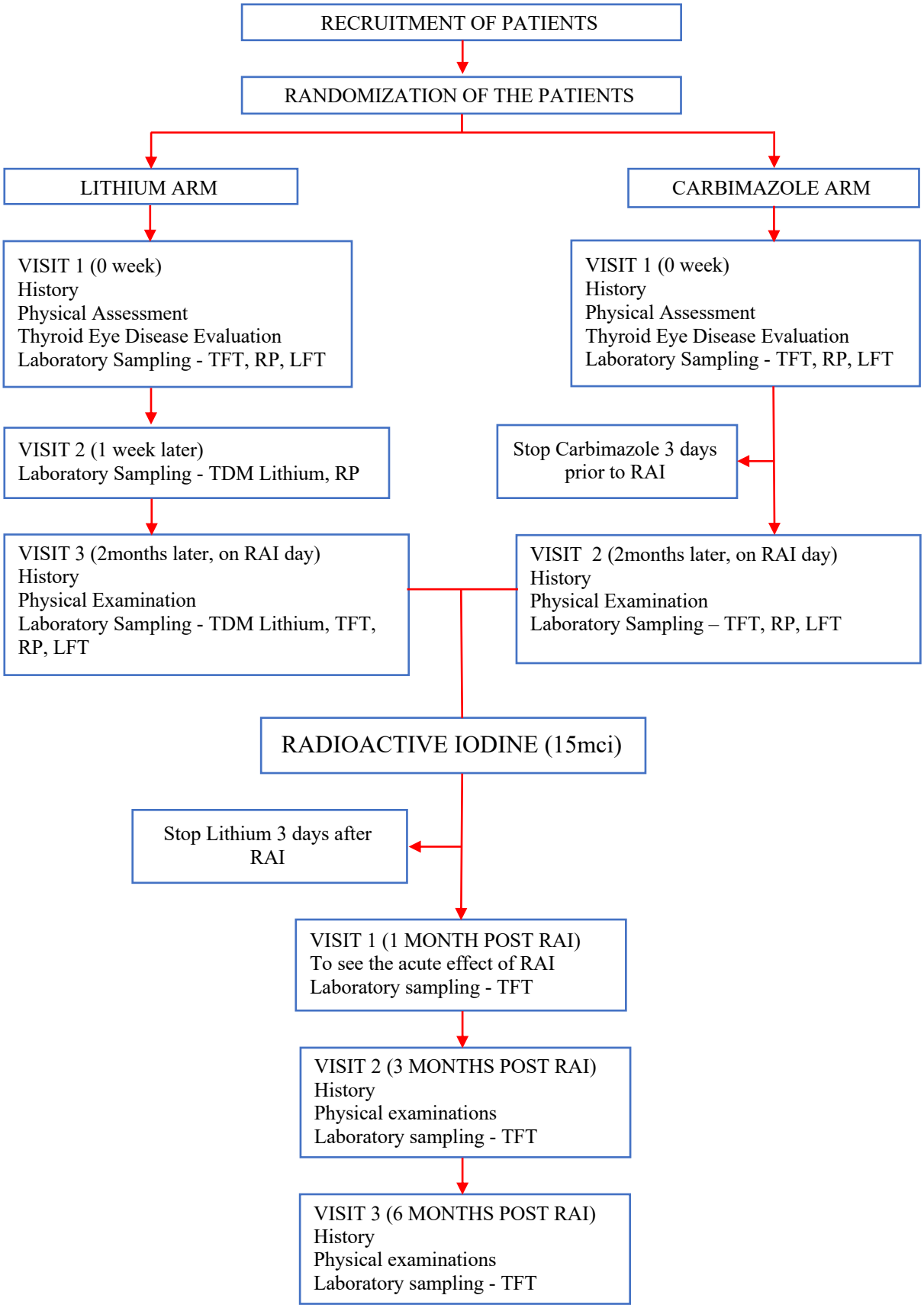
1. Selective serotonin reuptake inhibitors (SSRI)
2. Monoamine oxidase inhibitors (MAOIs)
3. Tricyclic antidepressant (TCA)
4. Anticonvulsants
5. Methyldopa
6. Methylxanthine
7. Muscle relaxants
8. Non-steroidal anti-inflammatory drugs (NSAIDs)
9. Phenothiazines
10. Tramadol
11. Diuretics
12. Acetazolamide
13. Anticonvulsants
14. Antipsychotic

Appendix 2

GANTT CHART

Year	2020			2021				2022			
	Oct	Nov	Dec	Jan	Jun	Sep	Dec	Jan	Mar	Jun	Sep
Proposal Presentation											
Ethical Submission and Approval											
Recruitment											
Data Collection											
Data Analysis											
Writing and publication											

STUDY FLOW CHART



Appendix 4

ESTIMATED BUDGET PROPOSAL

No	Description	Price per unit (RM)	Quantity	Total amount (RM)
1.	Blood test TFT TDM Lithium Renal profile Liver function test	 34 4 13 16	 430 86 258 172	 14 620 344 3 354 2 752
2.	Radioactive Iodine	405	86	34 830
			TOTAL	**55 900**