TABLET - Summary of Protocol Amendments

Amendment Number	Protocol Version	Description
1	2.0	Changes to current Protocol 1. Protocol Version 2.0 Addition of members to steering committee and DMC. 2. Protocol Version 2.0 Addition of two further exclusion criteria. a) Women who intend to conceive using ovulation stimulation therapy. Women with ovulation stimulation treatment will have a very different hormonal milieu to those without ovarian stimulation. Thus the endocrinologists (and in fact one of the EME reviewers) suggested excluding these patients. b) Women with previous or current cardiac disease. Thyroxine has the effect of increasing heart rate, and will need to be carefully titrated in patients with cardiac disease. Thus this trial will not be suitable for them. 3. Protocol Version 2.0 Addition of Roche Cobas Analyser to specified Analysers for trial participation. 4. Protocol version 2.0 Additional appointment at 9 months post randomisation and pre-pregnancy to dispense a further 3 month supply of trial medication. This was previously covered by an appointment at 3 months post randomisation and pre pregnancy, where 6 months of medication was dispensed in one appointment. This extra appointment will overcome any potential problems involving drug expiry date of the IMP or Placebo and would also enable the trial investigators to meet with the participant and discuss any trial related issues. 5. Protocol version 2.0 Addition of collection of anonymised excess serum to be used for quality control purposes, and possible future analyses of other biomarkers, which we understand will require separate ethical approval. 6. Protocol Version 2.0 Minor changes in spelling, typos and table/section references.
2	3.0	Changes to current Protocol 1. Protocol version 3.0 section 4.2 page 10 In a double blind study there is no risk of foreknowledge, and therefore the sentence has been revised to read more clearly. 2. Protocol version 3.0 Section 5.1.4 page 11 Revision of word "given" to "taken" as the capsule will be self-administered. The following sentence "A sheet giving instructions on how to take the capsules, and what to do if a capsule is missed, will be given to the participant at the randomisation appointment." has been inserted to inform of instructions sheet to take medication included in this submission. Deletion of sentence referring to attending clinician, as participant will be outpatient.

		Protocol Version 3.0 section 5.3 page 12 re-arrangement of sentence The Trial coordinator will monitor drug compliance with help from Pharmacy Accountability logs. Protocol Version 3.0 section 8.3.1 Page 22 - removal of sentences " The Trial Statistician may be unblinded to the level of groups A and B. A and B will be made know to the DMC if appropriate" In section 5.5.3 the Trial Protocol does not specify statistician in the list of blinded people. In order to produce DMC reports at the A/B level, the trial Statistician would not be blinded. The following sentence has also been removed in line with this change. **<u>Non- Substantial Changes</u>** Protocol version 3.0: Page ii/iii Update of titles from Dr to Professor. Page ii Change of IT contact and details. Page iii Insertion of ISRCTN number. Page 28 Reference 5 updated from (in press).
5	4.0	<u>Changes to current Protocol</u> 1. Target the Infertility population for screening and recruitment. 2. To increase the range of TFT analysers which are permitted for the trial. These are broadly the most frequently used analysers in the country. This will enable us to recruit from a wider range of centres. We have found that restricting to the Roche Analysers very limiting, meaning that other keen hospitals are not been given an opportunity to participate in the trial. The reference ranges for each analyser will be determined by the thyroid experts on the TMG. We feel that this change presents an opportunity to reflect the general UK population in the trial. To account for the variation in analysers we have also widened the Free T4 range Inclusion Criteria range to be between 10.0 to 21.0 pmol/L. Other changes which have also been incorporated into this submission. 3. To allow for blood for screening to be taken at the first approach to the patient. (This is mainly at the request of the patients who would prefer their blood sample to be taken immediately with other bloods rather than having to return for a blood sample) 4. Removal of a DMC Member who has resigned from the trial DMC due to increasing trial commitments. (A replacement is being sought). 5. Listing specific examples of conditions which are **not** required to report an SAE.
21	5.0	<u>Study Extension</u> This study has been extended to December 2015. <u>Changes to current Protocol</u> 1. TABLET Trial Management and Steering Group and Trials Office Team There have been a number of changes to members and their locations. Protocol Section: 3.1. 2. As timeframes for initial patient contact are short, and patients may be distressed, there are times when the patient is discharged before contact is made, even though they are aware of the trial. We wish to be able to contact the patient following discharge. 3. Protocol Section 3.2 We must exclude women with a current thyroid disorder, but do not want to exclude

		all women who have required only short-term treatment a significant time ago. It would be difficult to propose criteria for inclusion, so we propose that the small number of women who fall into this category are considered on a case by case basis, with discussion between the local PI and chief investigator. There is no safety reason to exclude these women. 4. Protocol Section: 3.3 Patients who are initially screened for the trial are sometimes not contactable by telephone or will not answer calls from private numbers on their mobile phones. We wish to introduce a letter, to have the ability to contact patients with normal blood results by letter. We have introduced Patient Normal Results Letter v1.0 16/2/15 and amended the word "telephone" to "contact" in the Patient Screening Leaflet so it is now v5.0 16/2/15. 5. Protocol section: 4.1 Clarification that a trial number and treatment bottle are not allocated until all essential information is entered on to the randomisation database. 6. Protocol section 4.2 We are explicitly mentioning that the randomisation algorithm will be minimised by centre. Given the study is double blind we do not believe this will be an issue. 7. Protocol Sections: 5.1.3 and 5.2.2 The name of the drug supplier has changed from Bilcare to Sharp Clinical, following a corporate merger, but the manufacturing authorisation has been transferred to the new legal entity. We wish to update the Protocol to reflect this change. The Marketing authorisation holder has changed to Mercury Pharma. 8. Protocol Section 5.2.1, 5.3, 7.6.1, 7.10. Adding the term pregnancy loss to clarify that all forms of pregnancy loss constitute an outcome of trial and that trial participation and trial drug use cease at this point. 9. Protocol Section: 5.3 In a measure to gather good compliance data we are asking the trial participant a question on estimated percentage of time the IMP is taken, in addition to pill counting. 10. Protocol Sections: 5.5.1 and 5.5.2 To clarify the clinical management of thyroid problems which are identified within the trial, we have re-worded some sections of the protocol and refer clinicians to guidance agreed by the TMG. We wish to promote discussion of these cases with clinical members of the TMG. 11. Protocol sections 5.5.3 Link to online TABLET code-break system https://www.trials.bham.ac.uk/TABLET 12. Protocol section 9.2 In order to clarify the central monitoring approach adopted by the trial section 9.2 has been re-worded. <u>Non Substantial Changes</u> SMPC for the IMP (SMPC v2,0).
22	6.0	<u>Changes to the Protocol</u> 1. Updated version 6.0 24th June 2015. 2. Contents page amended to list Appendix I Summary of Product Characteristics. 3. Section 6.1.4 changed wording. 4. Appendix I changed wording to replace page on expected toxicities.

		Non Substantial Changes SmPC v3.0 24th June 2015 SmPC v4.0 25th June 2015 SmPC v5.0 26th June 2015
24	6.1	Changes to current Protocol Update the SmPC for the trial IMP Levothyroxine to 6.0.
25	6.2	Changes to current Protocol 1. Section: 4.2 update to the stratification variables. 2. Sections: 5.1.3 clarification of the manufacturing authorisation holder to reflect the changes submitted in SA21.
26	7.0	Changes to current Protocol 1. Update to the Trial Management Group. 2. Section 3.4.2 – Clarification to the exclusion criteria. 3. Section 5.1.1 - Clarification of safety assessments. 4. Section 5.1.3- Clarification on storage of IMP. 5. Section 5.2.1 – Clarification of treatment duration. 6. Section 5.3 – Clarification of compliance monitoring. 7. Section 5.5 – Clarification of withdrawal process. 8. Section 6.1.2/6.1.3/6.3/6.4 – Clarification of reporting SUSARs. 9. Section 7 – Clarification of follow up and secondary measures. 10. Section 8.1 – Clarification of primary outcome measure. 11. Section 8.3 – Clarification of statistical analysis. 12. Section 9.4 – Clarification of Date Monitoring and Ethics Committee. 13. Appendix I – updated SmPC for Levothyoxine.