

**Randomized Evaluation of the Effects of
Anacetrapib through Lipid-modification
(HPS3/TIMI55 – REVEAL): Post Trial Follow Up**

Data Analysis Plan

EDMS#6383

Version 1.0

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1 Version History

1.0	Initial Version	Created by Emily Sammons, Martin Landray, Louise Bowman, and Jemma Hopewell Reviewed and approved by Steering Committee (29th July 2019) Released: (30 th July 2019)
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2 Introduction

Title: Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (HPS3 / TIMI55 – REVEAL): Post-Trial Follow-Up
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ISRCTN number: 48678192
Sponsor: Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), University of Oxford
Funder: Merck Sharp & Dohme (Merck)

2.1 Background

This Data Analysis Plan describes the strategy, rationale and statistical methods that will guide assessment of the clinical efficacy and safety of anacetrapib in the in-trial and two-year, off-treatment post-trial follow-up (PTFU) of the REVEAL trial. Details of the REVEAL trial have been published elsewhere^{1,2} and elaborated in the Post-trial Follow-up Plan which was finalised in May 2016 at which point the Steering Committee, funders and investigators remained blind to the main trial results. This Data Analysis Plan was finalised in July 2019 at which point the Steering Committee, funders and investigators remain blind to results from the PTFU period.

The PTFU Plan identified the following main outcomes of interest:

- i) Mortality (from all causes combined and, separately, within particular categories of causes, including cardiovascular and non-vascular causes);
- ii) Cancer at all sites (fatal or non-fatal), and site-specific cancers considered separately (excluding any known to pre-date randomization and non-melanoma skin cancers);
- iii) Cardiovascular events; and
- iv) Other serious adverse events (overall and, separately, by type).

In addition, exploratory assessments will be made of other possible effects of anacetrapib among particular subgroups of participants based on data recorded at the randomization visit (as specified in the main protocol), and on other serious adverse events during the extended follow-up period.

3 Roles and Responsibilities

All analyses for reports, presentations and publications will be prepared by the coordinating centre at the Clinical Trial Service Unit, University of Oxford (the regulatory sponsor of the REVEAL trial).

4 Comparisons of Anacetrapib vs. Placebo

All analyses will involve intention-to-treat comparisons of outcomes during full follow-up period (unless otherwise stated) among all those participants allocated at randomisation to receive anacetrapib 100mg daily versus all those allocated to receive matching placebo. Analyses will be of the first occurrence of the specified outcome. For those events that were subject to adjudication (see Protocol and PTFU Plan), analyses include all confirmed and unrefuted events.

Full follow-up period: The Full Follow-up Period is defined as the time from randomization until the end of the Post-trial Follow-up Period unless censored earlier according to the rules described in [Appendix A](#)):

4.1 Key Efficacy Analyses pre-specified in Trial Protocol

The following analyses were pre-specified in the main protocol prior to study start.

4.1.1. Primary Assessment

The primary assessment will involve an intention-to-treat comparison among all randomized participants of the effects of allocation to anacetrapib versus placebo on the incidence of major coronary events (defined as the occurrence of coronary death, myocardial infarction or coronary revascularization procedure) during the full follow-up period.

4.1.2 Secondary Assessments

Secondary assessments will involve intention-to-treat comparisons among all randomized participants of the effects of allocation to anacetrapib versus placebo during the full follow-up period on:

- (i) Major atherosclerotic events (defined as coronary death, myocardial infarction or presumed ischaemic stroke; the key secondary outcome);
- (ii) Presumed ischaemic stroke (i.e. not known to be haemorrhagic); and
- (iii) Major vascular events (defined as coronary death, myocardial infarction, coronary revascularization or presumed ischaemic stroke).

4.1.3 Additional Assessments

These assessments (which were specifically requested prior to the start of the study by regulatory agencies) will involve intention-to-treat comparisons among all randomized participants of the effects of allocation to anacetrapib versus placebo during the full follow-up period on:

- (i) Cardiovascular death or myocardial infarction; and
- (ii) Cardiovascular death, myocardial infarction or stroke.

4.2 Key Post-trial Follow-up analyses

The following analyses were specific in the Post-trial Follow-up Plan finalised in May 2016 prior to unblinding of the main trial results.

4.2.1 Mortality

Assessments of mortality will involve intention-to-treat analyses among all randomized participants of the effects of allocation to anacetrapib versus placebo during the full follow-up period on:

- (i) Mortality from all causes combined
 - (ii) Mortality within particular categories of causes, as follows:
 - all cardiovascular causes combined; and, separately:
 - coronary (including sudden cardiac death)
 - other cardiac
 - stroke
 - other vascular
 - all non-cardiovascular causes combined; and, separately:
 - cancer
 - infection
 - respiratory
 - hepatic
 - other medical*
 - non-medical
- * including undetermined cause

4.2.2 Cancer

Assessments of cancer (fatal or non-fatal combined, and excluding any known to pre-date randomization and non-melanoma skin cancers) will involve intention-to-treat analyses among all randomized participants of the effects of allocation to anacetrapib versus placebo during the full follow-up period on:

- (i) Cancer at all sites combined
- (ii) Cancer at particular sites:
 - gastrointestinal
 - respiratory
 - breast
 - melanoma
 - genitourinary
 - haematological
 - other or not specified

4.2.3 Cardiovascular events

4.2.3.1 Time-based analyses

Analyses will involve intention-to-treat analyses among all randomized participants of the effects of allocation to anacetrapib versus placebo on major coronary events, major atherosclerotic events, and major vascular events:

- (i) by year of follow-up during the full follow-up period
- (ii) during the in-trial and post-trial follow-up periods, separately
- (iii) occurring more than one year after randomization

4.2.3.2 Other cardiovascular events

Analyses will involve intention-to-treat analyses among all randomized participants of the effects of allocation to anacetrapib versus placebo during the full follow-up period on:

- (i) Coronary death or myocardial infarction, and, separately, myocardial infarction alone
- (ii) Stroke of any type combined; and, separately, of particular types, i.e.:
 - confirmed ischaemic stroke
 - confirmed haemorrhagic stroke
 - stroke of unknown/unconfirmed aetiology
- (iii) Coronary revascularization (including urgent and non-urgent coronary revascularization combined)
- (iv) Non-coronary revascularizations, including percutaneous interventions (with or without stenting), surgical revascularization procedures (e.g. grafting, endarterectomy), and amputation for presumed vascular disease
- (v) Combination of first and subsequent occurrences of the primary outcome

4.2.3.3 Exploratory analyses among patient subgroups

Exploratory assessments will be made of the effects of anacetrapib on major coronary events during the full follow up period among particular subgroups of participants based on data recorded at the randomization visit (as specified in the main protocol; see [Appendix B](#)).

4.2.4 Other serious adverse events

Assessments will involve intention-to-treat analyses among all randomized participants of the effects of allocation to anacetrapib versus placebo during the full follow-up period on serious adverse events (fatal and non-fatal combined) by MedDRA (version 14.0) System Organ Class (with exploratory analyses by Higher Level General Term and Higher Level Term)."

4.2.5 Exploratory Assessments

Post-hoc exploratory assessments will be made of other possible beneficial or adverse effects of anacetrapib during the combined in-trial treatment period and post-trial follow-up period.

5 Details of Analyses

5.1 Methods of Analysis

All participants randomized to anacetrapib will be compared with all participants randomized to placebo, regardless of whether a participant received all, some or none of their allocated treatment (i.e. intention-to-treat [ITT] analyses).^{3, 4} A participant may contribute to more than one assessment if they have events of more than one type (e.g. non-fatal ischaemic stroke followed by coronary death). For the time-to-event analyses, survival analytic methods will be used to evaluate the time to the first event during the full study period. For each outcome, log-rank method will be used to estimate the average event rate ratio comparing all those allocated active anacetrapib with all those allocated placebo. Estimates of the event rate ratio will be shown with 95% confidence intervals. Kaplan-Meier estimates for the time to each of the primary and secondary outcomes will also be plotted (with their associated log-rank p-values). Cox regression may be used where rate ratios are extreme (e.g. >2 or <0.5).

In all analyses, two-sided p-values (2P) <0.05 will be considered statistically significant (after any allowance for multiplicity as outlined in [section 5.2](#)). Recurrent events will be analysed using the negative binomial and sensitivity analyses will be performed using alternative methods such as permutation testing.

At the time of finalizing the Data Analysis Plan in July 2019, overall loss-to-follow-up at the end of the full follow-up period is minimal (2.2%), no exploratory analyses investigating the impact of missing data not at random/informative missingness are planned.

5.2 Allowance for Multiplicity of Comparisons

For all pre-specified analyses, allowance in their interpretation will be made for multiple hypothesis testing,^{3,4} taking into account the nature of events (including timing, duration and severity) and evidence from other studies. In addition to the pre-specified comparisons, many other analyses will be performed with due allowance for their exploratory and, perhaps, data-dependent nature. Conventionally, two-sided P-values <0.05 are often described as “significant”. But, the larger the number of events on which a comparison is based and the more extreme the P-value after any allowance has been made for the nature of the particular comparison (i.e. primary, secondary or tertiary; pre-specified or exploratory), the more reliable the comparison and, hence, the more definite any finding will be considered. Analyses of fatal events will be interpreted in the light of the observed effects on relevant non-fatal events.⁴

5.3 Tests for Heterogeneity of Effects

Tests for heterogeneity of the proportional effect observed in subgroups or by time period (e.g. in-trial vs. post-trial) will be used to determine whether the proportional effects in specific subcategories are clearly different from the overall effect^{3,4}. If, however, categories can be arranged in some meaningful order (e.g. years since randomization: 1, 2, 3, 4+ or age at randomisation: <65; ≥65<70; ≥70) then assessment of any trend will be made. Unless otherwise stated, those with missing values of baseline values will be included in the subgroup that includes the median (for continuous variables) or the largest group (for categorical variables), and the number of missing values will be clearly indicated.

When a number of different subgroups are considered, chance alone may lead to there being no apparent effect in several subgroups in which the effect of treatment really is about the same as is observed overall. In such circumstances, “lack of direct evidence of benefit” is not good “evidence of lack of benefit”, and clearly significant overall results would provide strong indirect evidence of benefit in some small subgroups where the results, considered in isolation, are not conventionally significant (or, even, perhaps, slightly adverse)³⁻⁵. Hence, unless the proportional effect in some specific subcategory is clearly different from that observed overall, the effect in that subcategory is likely to be best estimated indirectly by applying the proportional effect observed among all patients in the trial to the absolute risk of the event observed among control patients in that category.⁵

5.4 Coding and Categorisation of Adverse Events

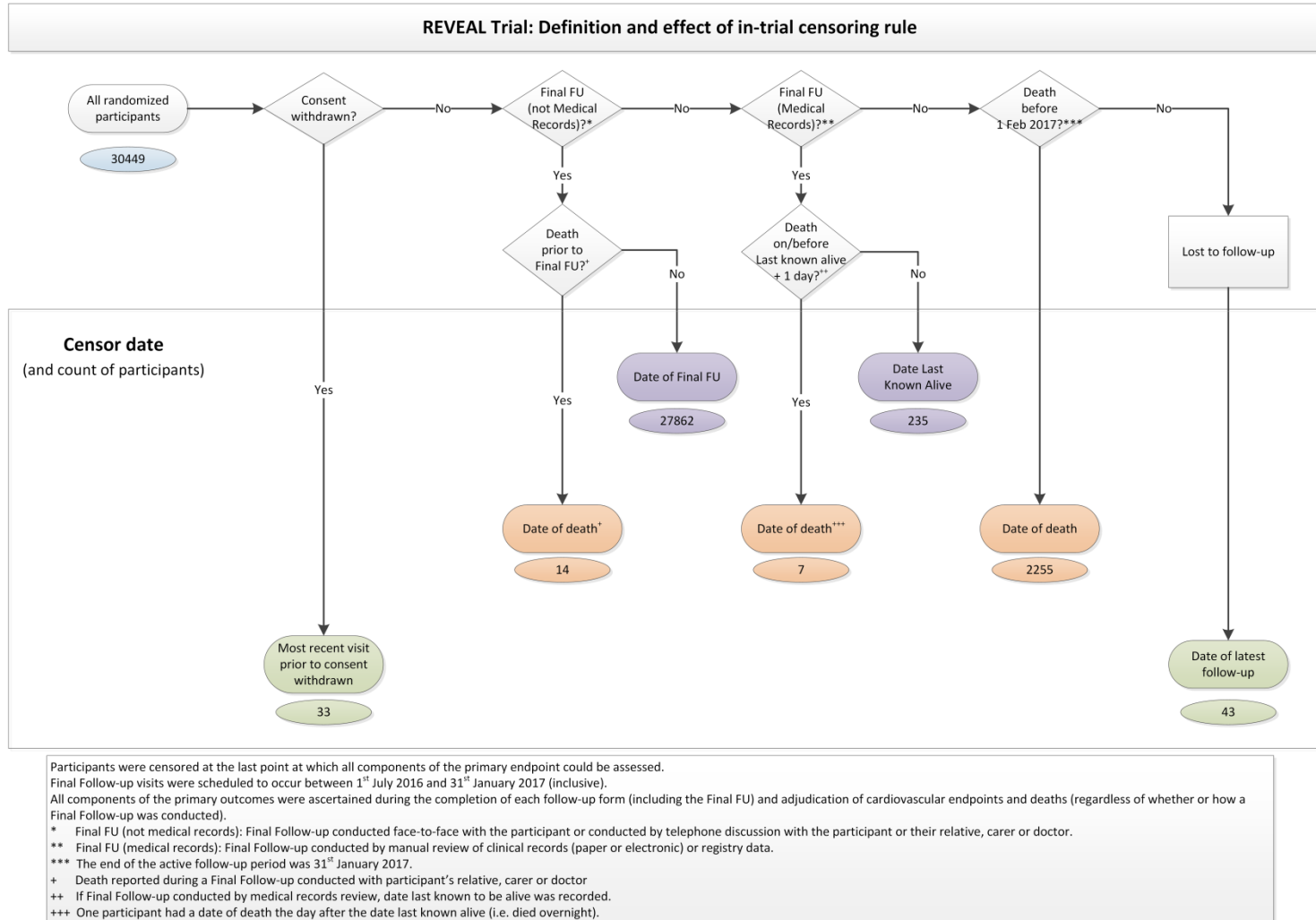
All adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 14.0. Unless otherwise stated, events are to be categorised according to System Organ Class.

6 References

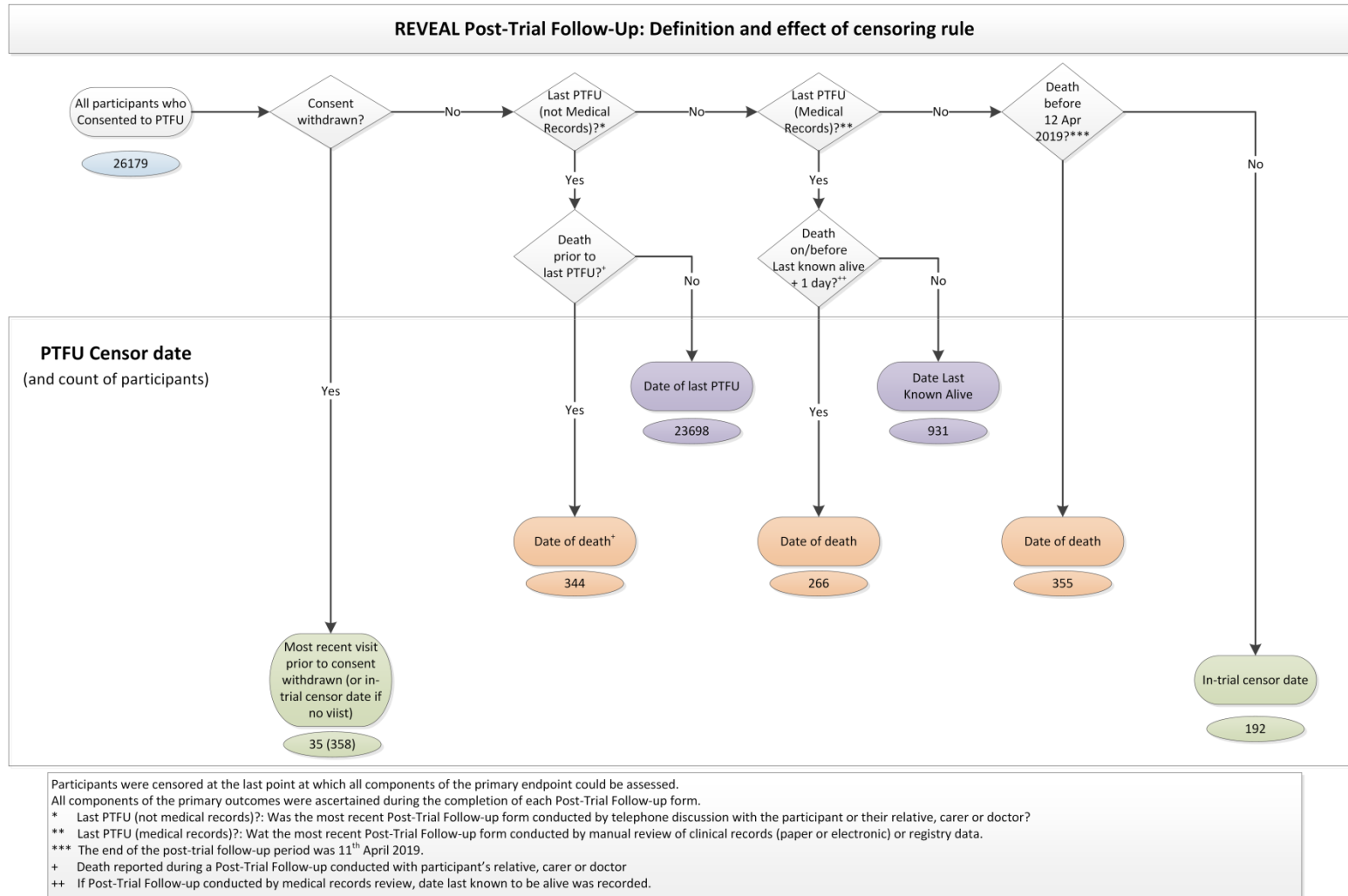
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3. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer*. 1976; **34**(6): 585-612.
4. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. *Br J Cancer*. 1977; **35**(1): 1-39.
5. Collins R, MacMahon S. Reliable assessment of the effects of treatment on mortality and major morbidity, I: clinical trials. *The Lancet*. 2001; **357**(9253): 373-80.

7 Appendix A: Censoring rules

(Note: Numbers shown are the number of randomized participants censored by each step of the rule. These are based on an analysis of provisional data conducted on 2nd July 2019.)



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8 Appendix B: Participant subgroups

The main protocol and Data Analysis Plan defined the following particular subgroups of participants based on data recorded at the randomization visit:

(i) Disease type prior to randomization:

- coronary heart disease
- cerebrovascular disease
- peripheral arterial disease
- diabetes*

and timing of most recent qualifying vascular event: <12; ≥12 months

* diabetes at randomization is defined as self-reported diabetes recorded on screening or randomization form; or diabetes-related adverse event recorded on or before date of randomization; or use of hypoglycaemic medication reported on randomization form

(ii) Three similar-sized groups based on lipid and lipoprotein measurements* from the Randomization visit:

- HDL cholesterol (mmol/L): <0.9; ≥0.9<1.1; ≥1.1
- LDL cholesterol (mmol/L): <1.4; ≥1.4<1.7; ≥1.7
- total cholesterol (mmol/L): <3.2; ≥3.2<3.7; ≥3.7
- non-HDL cholesterol (mmol/L): <2.2; ≥2.2<2.6; ≥2.6
- triglycerides (mmol/L): <1.2; ≥1.2<1.7; ≥1.7
- apolipoprotein B (mg/dL): <60; ≥60<70; ≥70
- apolipoprotein A1 (mg/dL) <110; ≥110<125; ≥125
- lipoprotein (a) (nmol/L): <15; ≥15<55; ≥55

* using results measured in the central laboratory

(iii) Various other categories of participant based on their Randomization visit values:

- age (years): <65; ≥65<70; ≥70
- sex: male; female
- region: North America; Europe; Asia
- blood pressure (mmHg):
 - systolic <125; ≥125<140; ≥140
 - diastolic <75; ≥75<85; ≥85
- kidney function
 - estimated Glomerular Filtration Rate (ml/min/1.73m²) derived using the CKD-EPI equation⁴: <60; ≥60
 - urinary albumin:creatinine ratio (mg/mmol): normo-albuminuria (<3); micro-albuminuria (≥3 <30); macro-albuminuria (≥30)
- alcohol intake: current drinker; former/never drinker
- cigarette smoking: current; former; never
- body mass index (kg/m²): <25; ≥25<30; ≥30
- waist:hip ratio: low (<0.87 in women; <0.94 in men); medium (≥0.87<0.93 in women; ≥0.94<1.00 in men); high (≥0.93 in women; ≥1.00 in men)
- history of heart failure: yes; no
- atorvastatin dose (mg): low (10 in China; 20 in rest of the world); high (20 in China; 80 in rest of the world)

(iv) presence and absence of other treatments used at the Randomization visit:

- angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers:

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- aspirin or other antiplatelet drugs
- diuretics
- calcium-channel blockers
- beta-blockers