TIME

STATISTICAL ANALYSIS PLAN

Study Title:	Treatment in Morning versus Evening Study (TIME)		
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		Signature	Date
Prepared by:	Dr Robin Young	Robin Young	29/06/22
	Robertson Centre for Biostatistics		
Approved by:	Prof Alex McConnachie		29/06/2022
	Assistant Director of Biostatistics, Robertson Centre for Biostatistics		
	Prof Tom MacDonald		29/06/2022
	Professor of Clinical Pharmacology and Pharmacoepidemiology, University of Dundee		

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1. INTRODUCTION

1.1. STUDY BACKGROUND

Hypertension is a major risk factor for cardiovascular disease and affects people worldwide. Antihypertensive medications have been in routine use since the 1960s, and there are now many agents licensed for use in hypertension. It is widely accepted that lowering elevated blood pressure leads to a reduction in risks of heart attacks, strokes and all-cause mortality. Research using 24hr blood pressure monitoring has suggested that night-time blood pressure may be a better predictor of risk than daytime. It is suggested that medications administered at bedtime may have a greater protective effect than the same medications taken in the morning.

1.2. STUDY OBJECTIVES

The question to be definitively answered is whether, in usual care, nocturnal dosing of antihypertensive medication is better than morning dosing for reducing cardiovascular events.

Secondary questions examine whether there are any downsides to nocturnal dosing. Will patients accept nocturnal dosing? Nocturnal diuretic use causing urinary symptoms is likely to be an issue; data on this and how it can be managed is being collected (patients attempt nocturnal diuretic dosing, if not tolerated, they try 6 pm and finally revert to morning dosing). Nocturnal hypotension and its consequences (falls, fractures) are also being addressed. A sub-study also collects data on home blood pressure control.

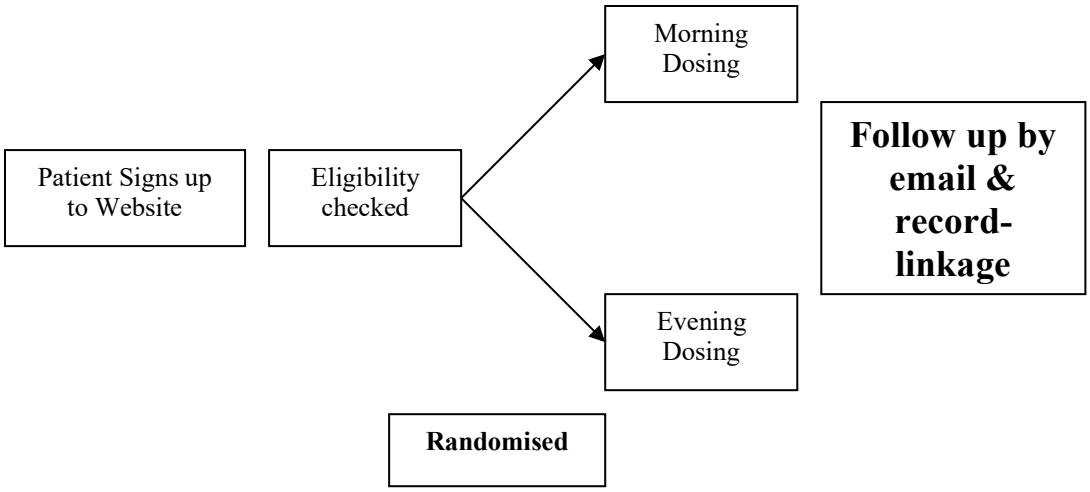
Finally, four other sub-studies will be conducted. One will assess any effects on cognitive function and the others self-reported sleep quality, mood and chronotype (tendency towards being a “morning” or “evening” person). These will be analysed separately to the main study analysis.

1.3. STUDY DESIGN

TIME is a prospective, randomised, open-label, blinded end-point (PROBE design) controlled clinical trial.

1.4. STUDY VISITS

The study will follow the following schematic:



1.5. SAMPLE SIZE

This sample size was adjusted during the study due to observed low cardiovascular event rates in several clinical trials involving similar populations. This adjustment was pre-specified in the published protocol[1].

For a 2-sided test to detect 20% superiority at 80% power, 631 events are needed. Based on the cardiovascular risk profile of participants recruited into the pilot phase of the study, a trial with a four year follow up period would need to randomise 19,740 participants. Because the primary analysis is intention to treat and because few participants are likely to withdraw consent for record-linkage follow up, only relatively minor (< 5%) inflation of the 19,740 participants was required to compensate. A target of 20,000 participants will be randomised. The original sample size estimate, based on a higher cardiovascular event rate was 10,269.

1.6. STUDY POPULATION

The study population includes adults (≥18 years) in the UK who have hypertension and are prescribed at least one antihypertensive drug. For full details, see study protocol.

1.7. STATISTICAL ANALYSIS PLAN (SAP)

1.7.1. SAP OBJECTIVES

The objective of this SAP is to describe the statistical analyses to be carried out for the final analysis of TIME. Any analyses that are undertaken and reported but not pre-specified in this SAP will be labelled as not pre-specified (post-hoc) in all reports.

1.7.2. GENERAL PRINCIPLES

The primary analyses specified in this SAP will be carried out according to the intention-to-treat (ITT) principle, i.e. according to randomised group allocation, regardless of compliance with morning or evening dosing.

Following completion of the analyses specified in this SAP, alternative analyses will be considered to estimate the effect of evening vs. morning dosing amongst those individuals who are compliant with their assigned regimen.

Data will be summarised as a whole and by randomised group. The number of observations and the number of missing values will be reported. Continuous measures will be summarised using mean, standard deviation, median, quartiles, and range. Categorical measures will be reported using frequencies and percentages. Survival data will be summarised as the number of first events, crude percentage with events, and rates of events per 100 person-years of follow-up.

1.7.3. STUDY PROTOCOL

The current study protocol at the time of writing is Version 12.0, dated 10th February 2021.

1.7.4. DEVIATIONS TO THOSE SPECIFIED IN PROTOCOL

None

1.7.5. SOFTWARE

Analyses will be carried out using R for Windows v3.4.1 or SAS for Windows v9.3, or higher versions of these programs.

2. ANALYSIS

2.1. ANALYSIS POPULATION

All analyses will include all randomised patients and all available follow-up time to estimate the expected effect of dosing time.

Patients will be censored in the survival analysis at the earliest of the following dates:

- Date of withdrawal of all consent to participate further in the study including withdrawal from record-linkage follow up (note that some patients can withdraw from email follow up but allow record-linkage follow up and these will not be censored).
- Date of death (if it is not part of the endpoint under consideration)
- Censoring date for analysis, taken as 31/03/2021

2.2. BASELINE CHARACTERISTICS

The following baseline characteristics will be tabulated:

- Demographics
  - Age
  - Sex

- Cardiovascular Risk Factors
  - Family History of cardiovascular disease
  - Systolic blood pressure
  - Diastolic blood pressure
  - Total cholesterol
  - BMI
  - Smoking status

- Medical History
  - Prior heart attack
  - Prior stroke
  - Impaired kidney function
  - Peripheral vascular disease
  - Any CVD (MI, CVA, PVD)
  - Diabetes
  - COPD
  - Chronic arthritis

- Medication use
  - Number of antihypertensive medications
  - Diuretic
  - ACE inhibitor
  - ARB
  - CCB
  - Beta blocker
  - Alpha-blocker
  - Other antihypertensive medication

2.3. EFFICACY OUTCOMES

2.3.1. PRIMARY OUTCOME

The primary outcome is the time to first event for the composite of vascular death, hospitalisation for non-fatal MI or non-fatal stroke.

A Cox Proportional Hazards model will be used to estimate the hazard ratio for evening vs morning dosing. The primary analysis will be unadjusted. The proportional hazards assumption will be assessed graphically using diagnostic plots. The estimated hazard ratio, 95% confidence interval and p-value will be reported. A cumulative incidence plot of events by treatment group will be produced.

2.3.2. PRIMARY OUTCOME – SUBGROUP ANALYSES

Subgroup analyses for the primary outcome will be performed for the following baseline characteristics:

- Age (above/below median)
- Sex (male/female)
- BMI (above/below median)
- Smoking status (current/former/never)
- Prior heart attack (yes/no)
- Prior stroke (yes/no)
- Cardiovascular disease (MI, CVA, PVD) (yes/no)
- Diabetes (yes/no)
- Number of antihypertensive medications (≤3/>3)
- Use of ACE inhibitor (yes/no)
- Use of ARB (yes/no)
- Use of ACE inhibitor or ARB (yes/no)
- Use of CCB (yes/no)
- Use of beta blocker (yes/no)
- Use of alpha-blocker (yes/no)

For each subgroup analysis, the primary analysis model will be extended to include the subgroup variable, plus the interaction between the subgroup variable and randomised group. Within-subgroup intervention effect estimates will be reported with 95% confidence intervals and p-values, and a likelihood ratio test p-value will be reported as a test of the interaction.

2.4. SECONDARY OUTCOMES

Secondary outcomes are the times to first event classified as:

- CV death
- Hospitalisation for non-fatal stroke
- Hospitalisation for non-fatal MI
- All-cause mortality
- Hospitalisation or death from congestive heart failure.

Statistical methods used will be as per the primary outcome. No pre-specified sub-group analyses will be performed for the secondary outcomes.

2.5. EXPLORATORY OUTCOMES

Exploratory outcomes will include:

- Stroke, by sub-type (ischaemic stroke, haemorrhagic stroke, subarachnoid haemorrhage, and other or non-specified)
- MI, by sub-type (total MI as well as the subgroups of STEMI and NSTEMI).
- Time to first reported non-adherence.

- Last known adherence at withdrawal, death, or end of trial (whichever is earliest).
- Home blood pressure readings submitted by a subset of participants will be averaged for each individual and treated as continuous variables (systolic blood pressure (SBP), diastolic blood pressure (DBP)). If times of readings are available, these data will also be graphically presented by time. We will test the following hypothesis:
    - Night-time dosing of antihypertensive medications will result in a lower Morning-Evening (ME) difference (morning BP - evening BP) when compared to morning-dosing.
- Antihypertensive medication expressed as the number of medications used will be compared between the randomised time of treatment groups at 3 monthly intervals.

2.6. SAFETY OUTCOMES

All pre-specified adverse events recorded by participants will be summarised by treatment group.

A table summarising pre-specified safety events (falls and fractures) by treatment group will be reported.

During the study, concern was expressed that night-time dosing of antihypertensive medications might increase the rate of diagnosis and progression of glaucomatous eye disease. We will therefore also report hospitalisations for glaucoma treatment by treatment group. Hospitalisations will be identified by either a) first diagnosis glaucoma, or b) glaucoma diagnosis in any position AND glaucoma-related surgical procedure.

3. TABLES AND FIGURES

The layout of the tables and figures will be agreed based on a report using dummy treatment codes prior to database lock. Approval of the format of this report will be documented separately.

4. LISTINGS

Not applicable. As this is not a CTIMP there will not be a listing of all adverse events.

5. DOCUMENT HISTORY

This is version 1.0 of the SAP for the TIME Study, dated 28th June 2022.

[1] Rorie DA, Rogers A, Mackenzie IS, Ford I, Webb DJ, Willams B, Brown M, Poulter N, Findlay E, Saywood W, MacDonald TM. Methods of a large prospective, randomised, open-label, blinded end-point study comparing morning versus evening dosing in hypertensive patients: the Treatment In Morning versus Evening (TIME) study. BMJ Open. 2016 Feb 9;6(2):e010313. doi: 10.1136/bmjopen-2015-010313. PMID: 26861939; PMCID: PMC4762112.