

BMJ Open Protocol for assessment of sleep quality and duration in the Treatment In Morning versus Evening (TIME) study: a randomised controlled trial using online patient-reported outcome measures

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ABSTRACT

Introduction We will use the existing online mechanisms of the Treatment in Morning versus Evening (TIME) study to collect patient-reported outcome measures of sleep quality to determine whether nocturnal dosing of antihypertensives affects sleep quality, when compared with morning dosing. The TIME study aims to determine if morning or evening dosing of antihypertensive medications is more effective in preventing heart attacks and strokes. The cardiovascular end points in TIME are identified by individual-level linkage to routinely collected hospital admissions and mortality data; these data are supplemented with participant-completed follow-up questionnaires, administered online. This substudy will provide information regarding the relative acceptability of morning and evening dosing of antihypertensives that will be essential should the TIME study results prompt doctors to consider advising particular dosing times to their patients.

Methods and analysis TIME participants are aged over 18 years and prescribed at least one antihypertensive drug, taken once a day. They are self-enrolled and consented on the secure TIME website (www.timestudy.co.uk) and then randomised to dosing time. Study follow-up is conducted by automated email. Average participant follow-up is expected to be 4 years. Participants in the sleep substudy are asked to complete an online sleep quality questionnaire at baseline, after 3 months and annually. This includes a Pittsburgh Sleep Quality Index (PSQI), a Hospital Anxiety and Depression Scale and an Epworth Sleepiness Scale. The primary outcome of the TIME Sleep substudy is sleep quality as measured by the PSQI. Secondary outcomes include sleep quantity and duration, and an analysis of any association between sleep quality and the main outcome measures of the TIME study (heart attack, stroke and vascular death).

Ethics and dissemination Ethical approval has been obtained from the Tayside Committee on Medical Research Ethics (MREC reference: 11/AL/0309), and results will be published in a peer-reviewed journal.

Protocol version 9 (approved 19 July 2017).

Strengths and limitations of this study

- This substudy will provide participant-derived information on the acceptability of morning and evening dosing of usual antihypertensives.
- The study uses an online patient-reported outcome measure to supplement a clinical primary end point.
- The participants are not blinded to dosing time allocation.

Trial registration number UKCRN ID: 17071. ISRCTN: 18157641. Pre-results.

INTRODUCTION

The Treatment In Morning versus Evening (TIME) study is a single-centre, online, parallel-group randomised controlled trial aiming to determine if morning or evening dosing of antihypertensive medications is better in terms of preventing heart attacks and strokes. It is not known what effect, if any, evening dosing of antihypertensives will have on sleep duration and quality. Significant adverse effects on sleep may greatly reduce the acceptance of any subsequent recommendation regarding antihypertensive dosing time.

Patient-reported outcome measures (PROMs) are increasingly being adopted by healthcare organisations¹ and researchers² as a way to demonstrate the effectiveness of interventions on outcomes that are best determined by patients themselves. Sleep quality is one such outcome that may have a bearing on any future application of dosing time guidance. Despite their potential, there are challenges associated with the administration of PROMs in clinical trials such as missing data

and inconsistent implementation. Early study dropout can be problematic when study participants are left to complete lengthy paper questionnaires without support or guidance. It has been suggested that electronic administration of PROMs may reduce such problems by automating reminders, standardising responses and allowing mandatory data fields.³ In this substudy, we aim to use the existing online follow-up mechanisms of the TIME study to collect PROMs of sleep quality. These will be used to determine whether nocturnal dosing of antihypertensives affects sleep quality, when compared with morning dosing.

The background to the main TIME trial is detailed in the main study protocol and is not repeated here.⁴ Links between sleep characteristics and hypertension have been extensively demonstrated.⁵ In particular, sleep disordered breathing, such as obstructive sleep apnoea, is an important cause of secondary hypertension and associated with increased cardiovascular risk.⁶ Furthermore, poor sleep quality and quantity have been shown to be associated with hypertension and the non-dipping phenomenon. Non-dipping describes a lack of the normal pattern of blood pressure lowering at night and has been found to be associated with increased risk of cardiovascular events in hypertensive patients.⁷ Non-dipping hypertensive patients are more likely to report poor sleep quality.⁸ The Saga Challenge Antihypertensive Study (S-CATS) suggested that effective hypertension treatment (with losartan and hydrochlorothiazide) also resulted in improvements in overall quality of life and sleep quality.⁹ The TIME study is based on research that suggests that evening dosing may be more effective at improving cardiovascular outcomes.¹⁰ One proposed explanation for this effect is that evening dosing of antihypertensives may restore the physiological nocturnal dipping pattern.¹¹ If this is the case then we might also expect evening administration of antihypertensive medication to result in some improvement in sleep quality. Conversely, some antihypertensive treatments have known adverse effects—that could be expected to worsen sleep quality when administered close to bedtime: polyuria caused by diuretics may increase night waking, and lipophilic beta-blockers have been implicated in parasomnia behaviours.^{12–14}

METHODS

Trial design

The TIME study is a parallel-group randomised controlled cardiovascular event outcome trial of people with treated hypertension. It aims to compare morning and evening dosing times of usual antihypertensive medication with a primary composite outcome of hospitalised heart attack, hospitalised stroke and vascular death. TIME is an online study with participants taking part via a secure study-specific electronic case report form.

The TIME Sleep substudy invites newly consented TIME study participants to complete an online sleep quality questionnaire at baseline (within 1 week of TIME study randomisation), 3 months and annually. The

questionnaire comprises the Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety and Depression Scale (HADS) and the Epworth Sleepiness Scale (ESS).

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) is a validated scoring system that has been used in many different clinical and research situations. It has been found to be effective at identifying poor sleep quality and detecting change in sleep quality. The PSQI overall score discriminates between 'good' and 'poor' sleepers. It also captures self-reported measures of sleep duration. The global score for the PSQI ranges from 0 to 21 with scores >5 having a sensitivity of 89.6% and specificity of 86.5% in identifying poor sleepers^{15 16} (see online supplementary appendix 1).

Hospital Anxiety and Depression Scale

Disordered mood is associated with poor sleep quality.¹⁷ In order to take this into account as a potential covariate in the final study analysis, participants were asked to complete a HADS. The HADS is a short (14-item) questionnaire that was first published in 1983 as a screening tool for depression and anxiety in general hospital populations.¹⁸ The tool has since been validated in many different clinical and community settings¹⁹ (see online supplementary appendix 2).

The Epworth Sleepiness Scale

The ESS is a short, self-administered, questionnaire that is widely used to assess daytime sleepiness. It is often used in clinical settings as a screening test for sleep disorders such as obstructive sleep apnoea syndrome^{20 21} (see online supplementary appendix 3).

Recruitment strategy

From August 2015 onwards, newly enrolled participants in the TIME study were offered the opportunity to volunteer for the sleep-quality substudy soon after they consented to take part in the main trial.

Intervention

Participants within the TIME study are randomly allocated to either morning or evening dosing of their usual antihypertensive medications. Subjects allocated to morning dosing are advised to take all of their blood pressure-lowering medications between 06:00 and 10:00 hours (and as soon after waking as practicable) throughout the study. Those allocated to evening dosing are instructed to take all their blood pressure-lowering medications between 20:00 and 24:00 hours (and as late before retiring as is practicable). There is no other intervention in the study and participants continue to attend their usual GP or outpatient clinic for routine hypertension follow-up. The only additional intervention within the sleep substudy is the questionnaires as described above.

Follow-up

TIME participants are asked by email to complete an online follow-up questionnaire every 3 months. This

questionnaire collects data on compliance, side effects and potential cardiovascular end point events. Additional sleep substudy follow-up email requests are sent 3 months after baseline sleep questionnaire submission and then annually.

Consenting participants

TIME participants were free to accept or decline the invitation to take part in the sleep substudy. To support their decision making, a patient information sheet was provided with the invitation containing detailed information about the substudy (see online supplementary appendix 4). All potential substudy participants have already completed an electronic consent form for the TIME study. They are asked to complete a further short online consent form for the substudy (see online supplementary appendix 5). This consent process is conducted entirely via the study website without the active participation of study personnel in general, although participants are given opportunities to clarify or ask for more information.

Data collection

The TIME Sleep substudy does not collect any additional data to the TIME study other than that obtained by the online sleep questionnaire.

Withdrawal

Subjects are free to withdraw from the TIME Sleep substudy at any point without affecting their participation in the TIME study overall.

Randomisation

Computer randomisation

Randomisation to the TIME study is done centrally using randomly generated bits, which are then allocated to participants sequentially. Randomised status is confirmed by automated email sent to the participant. There is no further randomisation in the TIME Sleep substudy.

Treatment allocation

Dosing time allocation is not blinded.

Patient and public involvement

The sleep-quality substudy was initially prompted by comments from TIME study participants about anticipated or experienced changes in sleep quality on changing their dosage time. Patients were not involved in the design, recruitment or conduct of the study but feedback from study participants was used to improve the online user interface of the substudy. Results of the sleep-quality substudy will be shared with participants by email.

STUDY POPULATION

Hypertensive patients aged 18 years or over, in the UK, prescribed one or more once-daily antihypertensive drug therapies, and, who have a valid email address.

TRIAL END POINTS

The end points of the TIME study are detailed in the published protocol.⁴

Primary end point

The primary end point of the TIME Sleep substudy will be the proportion of participants reporting poor sleep quality (defined as PSQI>5) at 3 months.

Secondary end points

- ▶ The proportion of participants reporting poor sleep quality at 1 year and annually.
- ▶ The proportion of participants reporting abnormal sleep duration at 3 months and annually.
- ▶ The mean change in sleep quality from baseline to 3 months and annually.
- ▶ The mean change in sleep duration from baseline to 3 months and annually.

We will also investigate whether any early changes in sleep quality or duration at 3 months are sustained in the long term and whether particular drug classes, for example, diuretics are more likely to affect sleep quality when taken at night than others. Additionally, we will determine if there is an association between non-adherence to dosing time and reported sleep quality and duration.

ADVERSE EVENTS

The TIME study will collect adverse events associated with changing the time of dosing. These data will be collected during follow-up and at time of withdrawal from the study using standard online questionnaires. No additional adverse event reporting will be undertaken in the sleep substudy.

STATISTICS AND DATA ANALYSIS

The primary analysis will be a comparison of sleep quality at 3 months in morning versus evening dosing. It will use a per-protocol cohort excluding patients who reported non-adherence to dose time allocation, died and/or were lost to follow-up. The outcome in this analysis (sleep quality defined as PQSI>5) is binary and we will use logistic regression to test for an effect of morning versus evening dosing, with baseline demographic variables (age, sex, systolic blood pressure, diastolic blood pressure, total cholesterol, body mass index (BMI), smoking status), self-reported medical history (heart attack, stroke, diabetes), baseline medication use (diuretics, ACE inhibitors, number of agents) and HADS score as covariates in the model.

Similar models will also be used for binary secondary outcomes. Change in sleep quality (PSQI score) and sleep duration will be treated as continuous variables with normal errors unless their distributions suggest this is inappropriate. We will test for interactions between any time of dose effect and medical history (previous myocardial infarction,

previous stroke, diabetes), class of antihypertensive medication and risk of sleep disordered breathing (using ESS, BMI, age and gender) will be performed. We will also correlate sleep data with TIME study outcomes (risk of heart attack, stroke or cardiovascular mortality) and assess whether any relationships are modified by dosing time.

Data collection and retention

This substudy will only capture data directly from participants. Data will be validated at point of entry into the TIME database and before final analysis. All data will be held securely within the Medicines Monitoring Unit at Ninewells Hospital and Medical School. To enable evaluations and/or audits, the investigators will keep records, including the identity of all participating patients, all original informed consent data, adverse event data and any source documents. The records will be securely retained and archived by the study sponsor according to ICH Good Clinical Practice (GCP) and local regulations.²² Participating subjects will be able to have sight of their own data on request and will be allowed to comment on perceived inaccuracies therein.

Data protection

The study will comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to appropriate study staff. Published results will not contain any personal data that could allow identification of individual participants.

Sample size: evidence of feasibility and power calculation

This sleep substudy is powered for the primary analysis of the difference in the proportion of patients in each group with poor sleep quality at the 3-month follow-up. A previous study in a non-clinical population reported that 34.5% of subjects met the proposed cut-off of 5 on the PSQI scale for poor sleepers.²³ Recruiting 1842 patients from each intervention group (3684 in total) will allow a difference in the proportion of patients reporting poor sleep of 5% between the two groups (30% vs 35%) with 90% power at the 5% level. Based on the current drop-out rate of the TIME study, 5%, we aimed to recruit 3878 people (actual recruitment was 3727 people). Such numbers would ensure that secondary analyses are amply powered when using the PSQI score as an outcome.

COMPETING STUDIES

We are not aware of any competing studies that would conflict with the TIME Sleep substudy.

Early stopping

If the event rate in the TIME study is higher than expected, or the TIME study Data Safety and Monitoring Board (DSMB) advise, then the trial may be stopped early. Sleep substudy data will not routinely be shared with the DSMB.

ETHICS AND DISSEMINATION

Steering committee and independent data monitoring committee

The TIME steering committee oversees the appropriate scientific and ethical conduct of the trial, provides advice to the study sponsor, advises on the conduct and analysis of the study and approves all publications and substudies. The committee will operate through meetings, teleconferences and e-mailings. The steering committee will be made up of invited experts, the chief investigator, the chair of the end point committee plus the coapplicants. The steering committee will meet at least annually. An independent data monitoring committee comprises experts in the field including clinicians with experience in hypertension and an expert trial statistician. The committee receives unblinded data and has the power to recommend modifications to the conduct of the study, including early discontinuation based on a risk/benefit assessment of the study data. It will meet at least annually and report to the steering committee.

Sponsorship: monitoring, audit, quality control and quality assurance

The study sponsor is the University of Dundee who undertakes monitoring and quality assurance. The TIME study is funded by the British Heart Foundation.

Protocol amendments

Changes in research activity, except those necessary to remove an apparent, immediate hazard, will be reviewed and approved by the chief investigator and sponsor. Amendments to the protocol will be submitted in writing for approval by the appropriate regulatory and ethical authorities prior to implementation.

Collaborating investigators

Collaborating investigators were responsible for dealing with the local issues of bringing the TIME trial to the attention of possible subjects either in clinics or in primary care.

Confidentiality

All data will be held securely with restricted access. Clinical information will not be released without the written permission of the participant, except as necessary for auditing by the sponsor, its designee, regulatory authorities or the research ethics committee.

Trial registration number

TIME is registered as ISRCTN: 18157641 and with a UKCRN ID: 17071. The trial is performed in line with GCP guidelines and International Society of Pharmacoeconomics Good Pharmacoeconomics Practice Guidance.^{22 24}

Dissemination

The results of the trial will be published in a peer-reviewed scientific journal and made available to participants.

DISCUSSION

There are some limitations to this methodology. The online version of the included PROMs has not been specifically validated against the original paper-based questionnaires. We endeavoured to minimise variation by closely replicating all questions and accompanying texts. The questionnaires were presented in single page format with the most significant difference from the original being the use of mandatory data fields to minimise missing data. As with all patient-reported outcomes, the tests may be subject to bias with respondents able to inflate or minimise their answers. Ideally, we would have used actigraphy to assess the accuracy of self-reported sleep duration, but this was beyond the resources of the study. As the dosing time allocation in the TIME study is not blinded, this must be taken into account in the interpretation of results. Only participants in the TIME study were eligible to take part. This means that the results of the substudy may not be generalisable; in particular, shift workers and those without a valid email address were excluded.

While observational data have found associations between sleep quality and duration and various cardiovascular diseases, the issue of how cardiovascular medications might affect sleep has not been widely explored. Additionally, case reports and cohort studies suggest that some specific blood pressure medications may be associated with sleep disturbance. The TIME Sleep substudy offers an opportunity to collect self-reported measures of sleep quality from a large trial population taking a wide range of antihypertensive medications. The TIME methodology facilitates the collection of additional participant-reported information like this to answer related research questions with minimal additional resources. The TIME Sleep substudy will be a very large study of sleep quality and duration in treated hypertensive adults that uses an online methodology to efficiently combine PROM data with clinical outcomes.

If the TIME study does show clinically significant benefits of dosing antihypertensive medication in the evening, this would represent a very cost-effective advance in the treatment of hypertension and the prevention of cardiovascular disease. However, successful implementation of any dosing time guidance based on the TIME results will depend on whether the dosing time is acceptable to patients. Sleep quality may play an important role in this assessment.

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Collaborators Key TIME Study Contacts: Chief Investigator—Thomas MacDonald (Dundee), Steering Committee—Independent Chair: Neil Poulter (London). Members: Thomas MacDonald (Dundee), Isla Mackenzie (Dundee), Evelyn Findlay (Dundee), Ian Ford (Glasgow), David Webb (Edinburgh), Bryan Williams (London) and Morris Brown (Cambridge). Independent Data Monitoring Committee—Chair: Peter Sever (London), Kausic Ray (London), Francesco Cappuccio (Warwick), Stuart Pocock (London). Co-ordinating Centre—Project Manager: Geraldine Mackle

(Dundee), Research Administrator: Catriona Young (Dundee). Data Management and Software—David Rorie (Dundee).

Contributors The idea for the substudy was conceived by AR. The substudy was developed further with assistance from TMM, ISM and IM. DAR programmed the online study website and maintains the follow-up system. The initial draft of the present manuscript was written by AR and circulated to DAR, ISM, IM and TMM for critical revision. All authors approved the final version of the manuscript.

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Competing interests None declared.

Ethics approval Approval was obtained from the Tayside Committee on Medical Research Ethics. MREC reference: 11/AL/0309.

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