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Assessment of Sleep Quality in the Treatment In Morning versus Evening (TIME) study using online Patient Reported Outcome Measures

Protocol of the TIME sleep substudy.

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ABSTRACT

Introduction

We will use the existing online mechanisms of the TIME (Treatment in Morning vs Evening) study to collect patient reported outcome measures of sleep quality to determine whether nocturnal dosing of antihypertensives affects sleep quality, when compared to 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 endpoints 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 sub-study 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 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 sub-study 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 (HADS) and an Epworth Sleepiness Scale (ESS). The primary outcome of the TIME Sleep sub-study 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.

Abstract word count: 298

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This sub-study 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 endpoint.
- The participants were not blinded to dosing time allocation.

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 organisations[1] and researchers[2] 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 drop-out 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 sub-study we aim to use the existing online follow-up mechanisms of the TIME study to collect Patient Reported Outcome Measures (PROMs) of sleep quality. These will be used to determine whether

nocturnal dosing of antihypertensives affects sleep quality, when compared to 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] 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.[6] Non-dipping hypertensive patients are more likely to report poor sleep quality.[7] The S-CATS study suggested that effective hypertension treatment (with losartan and hydrochlorothiazide) also resulted in improvements in overall quality of life and sleep quality.[8] The TIME study is based upon research that suggests that evening dosing may be more effective at improving cardiovascular outcomes.[9] One proposed explanation for this effect is that evening dosing of antihypertensives may restore the physiological nocturnal dipping pattern.[10] 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.[11–13]

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 (eCRF).

The TIME Sleep sub-study invites newly consented TIME study participants to complete an online sleep quality questionnaire at baseline (within one 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 0-21 with scores greater than 5 having a sensitivity of 89.6% and specificity of 86.5% in identifying poor sleepers.[14,15] (See appendix 1)

Hospital Anxiety and Depression Score

Disordered mood is associated with poor sleep quality.[16] In order to take this into account in the final study analysis, participants were asked to complete a Hospital Anxiety and Depression scale (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.[17] The tool has since been validated in many different clinical and community settings.[18] (See appendix 2)

The Epworth Sleepiness Scale

The Epworth Sleepiness Scale 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 (OSAS).[19,20] (See 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 sub-study 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 6am and 10am

throughout the study. Those allocated to evening dosing are instructed to take all their blood pressure lowering medications between 8pm and midnight. 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

Sleep sub-study 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 sub-study. To support their decision making, a patient information sheet was provided with the invitation containing detailed information about the sub-study (see appendix 4). All potential sub-study 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 sub-study (see 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 sub-study 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 sub-study 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 Sleep sub-study.

Treatment allocation

Dosing time allocation is not blinded.

STUDY POPULATION

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

TRIAL ENDPOINTS

The endpoints of the TIME study are detailed in the published protocol.[4]

Primary endpoint

The primary endpoint of the Sleep sub-study will be the proportion of participants reporting poor sleep quality (as measured by the PSQI) at 3 months.

Secondary endpoints will include:

- 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 longer term and whether particular drug classes e.g. diuretics are more likely to affect sleep quality when taken at night than others.

ADVERSE EVENTS

The TIME study will collect adverse events (AEs) 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 sub-study.

STATISTICS AND DATA ANALYSIS

The primary analysis will be a comparison of sleep quality at 3 months in morning versus evening dosing using a per-protocol analysis (excluding patients who report non-adherence to dose time allocation, deaths and patients lost to follow-up). Additionally, we will determine if there is an association between non-adherence to dosing time and reported sleep quality and duration. Secondary analyses will assess change in sleep quality and daytime sleepiness from baseline and over time in the two groups as measured by PSQI and Epworth Sleepiness Scale. Sub-group analyses, stratified by class of antihypertensive medication used, will be performed. The sleep data will also be compared with TIME study outcome data to assess if there is an association between sleep quality or duration and risk of heart attack, stroke or cardiovascular mortality.

Data collection and retention

This sub-study 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 (MEMO) 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.[21] 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 sub-study 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. [22] Recruiting 1,842 patients from each intervention group (3,684 in total), will allow a difference in the proportion of patients reporting poor sleep of 5% between the two group (30% versus 35%) with 90% power at the 5% level. Based upon 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 sub-study.

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 sub-study 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 sub-studies. 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 Endpoint Committee plus the co-applicants. The Steering Committee will meet at least annually. An independent data monitoring committee is completely independent and comprises experts in the field including clinicians with experience in hypertension and an expert trial statistician. The committee receives un-blinded 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 undertake 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.

Ethics

Ethical approval has been obtained from the Tayside Committee on Medical Research Ethics. MREC reference: 11/AL/0309.

Trial Registration

TIME is registered as ISRCTN: 18157641 and with a UKCRN ID: 17071. The trial is performed in line with Good Clinical Practice guidelines and International Society of Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practice Guidance.[21,23]

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. 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 sub-study may not be generalisable; in particular, shift workers and those without a valid email address were excluded.

While observational data has 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 sub-study offers an 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 sub-study 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. However, successful implementation of any dosing time guidance based upon the TIME results will depend on whether the dosing time is acceptable to patients. Sleep quality may play an important role in this assessment.

ABBREVIATIONS

AE	Adverse events
DSMB	Data Safety and Monitoring Board
ESS	Epworth Sleepiness Scale
GCP	Good Clinical Practice
GPP	Good pharmacoepidemiology practices
HADS	Hospital Anxiety and Depression Scale
OSAS	Obstructive sleep apnoea syndrome
PSQI	Pittsburgh Sleep Quality Index
PROM	Patient Reported Outcome Measure
TIME	Treatment In Morning versus Evening

Additional Information

Trial Registration: ISRCTN: 18157641.

Protocol Version: 9 (approved 19/07/2017)

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).

Contributorship statement: The idea for the sub-study was conceived by AR. The sub-study was developed further with assistance from TMM, ISM and IM. DR 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 DR,ISM,IM and TMM for critical revision. All authors approved the final version of the manuscript.

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Competing interests: There are no conflicts of interest.

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

Sponsorship: University of Dundee/NHS Tayside (TASC).

Trial Registration: UKCRN ID: 17071. ISRCTN: 18157641.

Provenance and peer review: Not commissioned;

Data sharing statement: Anonymised data from the study can be made available to bona fide researchers on application.

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PITTSBURGH SLEEP QUALITY INDEX (PSQI)

INSTRUCTIONS: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?

   USUAL BED TIME _____

2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

   USUAL GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

   HOURS OF SLEEP PER NIGHT _____

INSTRUCTIONS: For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...cannot get to sleep within 30 minutes	☐	☐	☐	☐
(b) ...wake up in the middle of the night or early morning	☐	☐	☐	☐
(c) ...have to get up to use the bathroom	☐	☐	☐	☐
(d ...cannot breathe comfortably	☐	☐	☐	☐
(e) ...cough or snore loudly	☐	☐	☐	☐
(f) ...feel too cold	☐	☐	☐	☐
(g) ...feel too hot	☐	☐	☐	☐
(h) ...had bad dreams	☐	☐	☐	☐
(i) ...have pain	☐	☐	☐	☐

(j) Other reason(s), please describe

_____

_____

How often during the past month have you had trouble sleeping because of this?	☐	☐	☐	☐

	Very good	Fairly good	Fairly bad	very bad
6. During the past month, how would you rate your sleep quality overall?	☐	☐	☐	☐

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	☐	☐	☐	☐
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	☐	☐	☐	☐

	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

	No bed partner or roommate	Partner/ roommate in other room	Partner in same room, but not same bed	Partner in same bed
10. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...loud snoring	☐	☐	☐	☐
(b) ...long pauses between breaths while asleep	☐	☐	☐	☐
(c) ...legs twitching or jerking while you sleep	☐	☐	☐	☐
(d) ...episodes of disorientation or confusion during sleep	☐	☐	☐	☐
(e) Other restlessness while you sleep; please describe	☐	☐	☐	☐

_____

_____

PSQI Page 2

SCORING INSTRUCTIONS FOR THE PITTSBURGH SLEEP QUALITY INDEX:

The Pittsburgh Sleep Quality Index (PSQI) contains 19 self-rated questions and 5 questions rated by the bed partner or roommate (if one is available). Only self-rated questions are included in the scoring. The 19 self-rated items are combined to form seven "component" scores, each of which has a range of 0-3 points. In all cases, a score of "0" indicates no difficulty, while a score of "3" indicates severe difficulty. The seven component scores are then added to yield one "global" score, with a range of 0-21 points, "0" indicating no difficulty and "21 " indicating severe difficulties in all areas.

Scoring proceeds as follows:

Component 1: Subjective sleep quality

Examine question #6, and assign scores as follows:

Response	Component 1 score
"Very good"	0
"Fairly good"	1
"Fairly bad"	2
"Very bad"	3

Component 1 score: _____

Component 2: Sleep latency

1. Examine question #2, and assign scores as follows:

Respo\nse	Score
≤15 minutes	0
16-30 minutes	1
31-60 minutes	2
> 60 minutes	3

Question #2 score: _____

2. Examine question #5a, and assign scores as follows:

Response	Score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Question #5a score: _____

3. Add #2 score and #5a score

Sum of #2 and #5a: _____

4. Assign component 2 score as follows:

Sum of #2 and #5a	Component 2 score
0	0
1-2	1
3-4	2
5-6	3

Component 2 score: _____

Component 3: Sleep duration

Examine question #4, and assign scores as follows:

Response	Component 3 score
> 7 hours	0
6-7 hours	1
5-6 hours	2
< 5 hours	3

Component 3 score:_____

Component 4: Habitual sleep efficiency

1. Write the number of hours slept (question #4) here:_____

2. Calculate the number of hours spent in bed:

Getting up time (question #3):_____

Bedtime (question #1):_____

_____

*Number of hours spent in bed:*_____

3. Calculate habitual sleep efficiency as follows:

(Number of hours slept/Number of hours spent in bed) X 100 = Habitual sleep efficiency (%)

(_____/_____) X 100 = %

4. Assign component 4 score as follows:

Habitual sleep efficiency %	Component 4 score
> 85%	0
75-84%	1
65-74%	2
< 65%	3

Component 4 score:_____

Component 5: Step disturbances

1. Examine questions #5b-5j, and assign scores for each question as follows:

Response	Score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

5b score: _____

5c score: _____

5d score: _____

5e score: _____

5f score: _____

5g score: _____

5h score: _____

5i score: _____

5j score: _____

2. Add the scores for questions #5b-5j:

Sum of #5b-5j: _____

3. Assign component 5 score as follows:

Sum of #5b-5j	Component 5 score
0	0
1-9	1
10-18-4	2
19-27	3

Component 5 score: _____

Component 6: Use of sleeping medication

Examine question #7 and assign scores as follows:

Response	Component 6 score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Component 6 score: _____

Component 7: Daytime dysfunction

1. Examine question #8, and assign scores as follows:

Response	Score
Never	0
Once or twice	1
Once or twice each week	2
Three or more times each week	3

Question#8 score: _____

2. Examine question #9, and assign scores as follows:

Response	Score
No problem at all	0
Only a very slight problem	1
Somewhat of a problem	2
A very big problem	3

Question #9 score: _____

3. Add the scores for question #8 and #9:

Sum of #8 and #9: _____

4. Assign component 7 score as follows:

Sum of #8 and #9	Component 7 score
0	0
1-2	1
3-4	2
5-6	3

Component 7 score: _____

Global PSQI Score

Add the seven component scores together:

Global PSQI Score: _____

Hospital Anxiety and Depression Scale (HADS)

Please answer the following questions about how you are feeling currently. Choose one response from the four given for each question. Try to give an immediate response and avoid thinking too long about your answers.

A	**I feel tense or 'wound up':**	
	Most of the time	3
	A lot of the time	2
	From time to time, occasionally	1
	Not at all	0

D	**I still enjoy the things I used to enjoy:**	
	Definitely as much	0
	Not quite so much	1
	Only a little	2
	Hardly at all	3

A	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0

D	**I can laugh and see the funny side of things:**	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3

A	**Worrying thoughts go through my mind:**	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not	1

	too often	
	Only occasionally	0

D	**I feel cheerful:**	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0

A	**I can sit at ease and feel relaxed:**	
	Definitely	0
	Usually	1
	Not Often	2
	Not at all	3

D	**I feel as if I am slowed down:**	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0

A	**I get a sort of frightened feeling like 'butterflies' in the stomach:**	
	Not at all	0
	Occasionally	1
	Quite Often	2
	Very Often	3

D	**I have lost interest in my appearance:**	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care as ever	0

A	**I feel restless as I have to be on the move:**	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0

D	**I look forward with enjoyment to things:**	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3

A	**I get sudden feelings of panic:**	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0

D	**I can enjoy a good book or radio or TV program:**	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

	Scoring (add the As = Anxiety. Add the Ds = Depression). The norms below will give you an idea of the level of Anxiety and Depression.	
	0-7 = Normal	
	8-10 = Borderline abnormal	
	11-21 = Abnormal	

Reference:

Zigmond and Snaith (1983)

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

Dear XXXX

Thank you for choosing to take part in the TIME study.

We are interested in potential ways that that taking your blood pressure medication at a certain time of day could affect your health and wellbeing.

One of the aspects that could be affected, positively or negatively, is sleep. We would like to invite you to take part in a questionnaire-based sub-study of TIME that will look at whether your sleep is affected by the time of dosage that you have been randomly allocated for the TIME study.

If you are interested in finding out more about this sleep quality sub-study, please click on the following link:

XXXXXXX

Your choice about whether to take part in this sub-study does not affect your participation in the main TIME study.

Thank you for your consideration,

The TIME study team

TIME Sleep Quality Sub-study: Informed Consent Form

(Standard yes/no tick box format)

I confirm that I have read and understood the *information sheet* for the above sub-study. I have had the opportunity to consider the information and ask questions, and have had these answered satisfactorily. Y/N

I understand that I will be sent emails asking me to complete an online questionnaire about sleep quality. Y/N

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. If I withdraw I understand that the sponsor will retain the data collected up to the point I withdraw. Y/N

I agree to take part in the TIME Sleep Quality Sub-study Y/N

Please enter your name to confirm that you have read the information sheet and answered the questions above. By entering the following information this will be equivalent to your signature on this consent form.

Forename _____ **Surname** _____

I have read, answered and understood all of the above questions and understand this is an electronic signature ☐

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	x
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,3
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	x
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	3
Introduction			

http://bmjopen-2018-021890 on 7 June 2018. Downloaded from

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	n/a
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	n/a
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4, 7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	x
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that	14

		limit such access for investigators	
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__n/a_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___11_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__n/a_____ __
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset and statistical code	___14_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___Y_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____n/a_____ __

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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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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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

Protocol of the TIME sleep sub-study.

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ABSTRACT

Introduction

We will use the existing online mechanisms of the TIME (Treatment in Morning vs Evening) study to collect patient reported outcome measures of sleep quality to determine whether nocturnal dosing of antihypertensives affects sleep quality, when compared to 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 endpoints 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 sub-study 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 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 sub-study 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 (HADS) and an Epworth Sleepiness Scale (ESS). The primary outcome of the TIME Sleep sub-study 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.

Abstract word count: 298

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This sub-study 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 endpoint.
- The participants were not blinded to dosing time allocation.

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 organisations[1] and researchers[2] 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 drop-out 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 sub-study we aim to

use the existing online follow-up mechanisms of the TIME study to collect Patient Reported Outcome Measures (PROMs) of sleep quality. These will be used to determine whether nocturnal dosing of antihypertensives affects sleep quality, when compared to 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 S-CATS study 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 upon 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 (eCRF).

The TIME Sleep sub-study invites newly consented TIME study participants to complete an online sleep quality questionnaire at baseline (within one 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 0-21 with scores greater than 5 having a sensitivity of 89.6% and specificity of 86.5% in identifying poor sleepers.[15,16] (See appendix 1)

Hospital Anxiety and Depression Score

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 Hospital Anxiety and Depression scale (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 settings.[19] (See appendix 2)

The Epworth Sleepiness Scale

The Epworth Sleepiness Scale 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 (OSAS).[20,21] (See 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 sub-study 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 6am and 10am (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 8pm and midnight (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 sub-study is the questionnaires as described above.

Follow-up

TIME participants are asked by email to complete an online follow-up questionnaire every three months. This questionnaire collects data on compliance, side effects and potential cardiovascular endpoint events. Additional sleep sub-study 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 sub-study. To support their decision making, a patient information sheet was provided with the invitation containing detailed information about the sub-study (see appendix 4). All potential sub-study 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 sub-study (see 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 sub-study 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 sub-study 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 Sleep sub-study.

Treatment allocation

Dosing time allocation is not blinded.

Patient and Public Involvement

The sleep-quality sub-study 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 sub-study. Results of the sleep-quality sub-study will be shared with participants by email.

STUDY POPULATION

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

TRIAL ENDPOINTS

The endpoints of the TIME study are detailed in the published protocol.[4]

Primary endpoint

The primary endpoint of the Sleep sub-study will be the proportion of participants reporting poor sleep quality (defined as PSQI>5) at 3 months.

Secondary endpoints will include:

- 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 longer term and whether particular drug classes e.g. 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 (AEs) 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 sub-study.

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 vs evening dosing, with baseline demographic variables (age, sex, systolic blood pressure, diastolic blood pressure, total cholesterol, BMI, smoking status), self reported past medical history (heart attack, stroke, diabetes), baseline medication use (diuretics, ACEi, 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 past medical history (previous MI, previous stroke, diabetes), class of antihypertensive medication, and risk of sleep disordered breathing (using Epworth sleepiness score, BMI, age and gender) will be performed. We will also correlate sleep data with TIME study outcomes (risk of heart attack, stroke of CV mortality) and whether any relationships are modified by dosing time.

Data collection and retention

This sub-study 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 (MEMO) 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 sub-study 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 1,842 patients from each intervention group (3,684 in total), will allow a difference in the proportion of patients reporting poor sleep of 5% between the two group (30% versus 35%) with 90% power at the 5% level. Based upon 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 sub-study.

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 sub-study 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 sub-studies. 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 Endpoint Committee plus the co-applicants. The Steering Committee will meet at least annually. An independent data monitoring committee is completely independent and comprises experts in the field including clinicians with experience in hypertension and an expert trial statistician. The committee receives un-blinded 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 undertake 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.

Ethics

Ethical approval has been obtained from the Tayside Committee on Medical Research Ethics. MREC reference: 11/AL/0309.

Trial Registration

TIME is registered as ISRCTN: 18157641 and with a UKCRN ID: 17071. The trial is performed in line with Good Clinical Practice guidelines and International Society of Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology 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 sub-study may not be generalisable; in particular, shift workers and those without a valid email address were excluded.

While observational data has 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 sub-study offers an 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 sub-study 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. However, successful implementation of any dosing time guidance based upon the TIME results will depend on whether the dosing time is acceptable to patients. Sleep quality may play an important role in this assessment.

ABBREVIATIONS

AE	Adverse events
DSMB	Data Safety and Monitoring Board
ESS	Epworth Sleepiness Scale
GCP	Good Clinical Practice
GPP	Good pharmacoepidemiology practices

HADS	Hospital Anxiety and Depression Scale
OSAS	Obstructive sleep apnoea syndrome
PSQI	Pittsburgh Sleep Quality Index
PROM	Patient Reported Outcome Measure
TIME	Treatment In Morning versus Evening

Additional Information

Trial Registration: ISRCTN: 18157641.

Protocol Version: 9 (approved 19/07/2017)

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).

Contributorship statement: The idea for the sub-study was conceived by AR. The sub-study was developed further with assistance from TMM, ISM and IM. DR 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 DR, ISM, IM and TMM for critical revision. All authors approved the final version of the manuscript.

Acknowledgments
With thanks to Stephen V Morant, statistical consultant, for his assistance in devising the statistical analysis plan. Thanks also to TIME study participants who have not only contributed their data but also provided invaluable feedback about study procedures and suggestions for improvements in the website user interface.

Funding: The TIME study is funded by a grant from the British Heart Foundation, Greater London House, 180 Hampstead Road, London, NW1 7AW.

Competing interests: There are no conflicts of interest.

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

Sponsorship: University of Dundee/NHS Tayside (TASC).

Trial Registration: UKCRN ID: 17071. ISRCTN: 18157641.

Provenance and peer review: Not commissioned;

Data sharing statement: Anonymised data from the study can be made available to bona fide researchers on application.

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PITTSBURGH SLEEP QUALITY INDEX (PSQI)

INSTRUCTIONS: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, when have you usually gone to bed at night?

   USUAL BED TIME _____

2. During the past month, how long (in minutes) has it usually take you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, when have you usually gotten up in the morning?

   USUAL GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

   HOURS OF SLEEP PER NIGHT _____

INSTRUCTIONS: For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...cannot get to sleep within 30 minutes	☐	☐	☐	☐
(b) ...wake up in the middle of the night or early morning	☐	☐	☐	☐
(c) ...have to get up to use the bathroom	☐	☐	☐	☐
(d ...cannot breathe comfortably	☐	☐	☐	☐
(e) ...cough or snore loudly	☐	☐	☐	☐
(f) ...feel too cold	☐	☐	☐	☐
(g) ...feel too hot	☐	☐	☐	☐
(h) ...had bad dreams	☐	☐	☐	☐
(i) ...have pain	☐	☐	☐	☐

(j) Other reason(s), please describe

_____

_____

How often during the past month have you had trouble sleeping because of this?	☐	☐	☐	☐

	Very good	Fairly good	Fairly bad	very bad
6. During the past month, how would you rate your sleep quality overall?	☐	☐	☐	☐

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	☐	☐	☐	☐
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	☐	☐	☐	☐

	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

	No bed partner or roommate	Partner/ roommate in other room	Partner in same room, but not same bed	Partner in same bed
10. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	☐	☐	☐	☐

If you have a roommate or bed partner, ask him/her how often in the past month you have had...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
(a) ...loud snoring	☐	☐	☐	☐
(b) ...long pauses between breaths while asleep	☐	☐	☐	☐
(c) ...legs twitching or jerking while you sleep	☐	☐	☐	☐
(d) ...episodes of disorientation or confusion during sleep	☐	☐	☐	☐
(e) Other restlessness while you sleep; please describe	☐	☐	☐	☐

_____

_____

SCORING INSTRUCTIONS FOR THE PITTSBURGH SLEEP QUALITY INDEX:

The Pittsburgh Sleep Quality Index (PSQI) contains 19 self-rated questions and 5 questions rated by the bed partner or roommate (if one is available). Only self-rated questions are included in the scoring. The 19 self-rated items are combined to form seven "component" scores, each of which has a range of 0-3 points. In all cases, a score of "0" indicates no difficulty, while a score of "3" indicates severe difficulty. The seven component scores are then added to yield one "global" score, with a range of 0-21 points, "0" indicating no difficulty and "21 " indicating severe difficulties in all areas.

Scoring proceeds as follows:

Component 1: Subjective sleep quality

Examine question #6, and assign scores as follows:

Response	Component 1 score
"Very good"	0
"Fairly good"	1
"Fairly bad"	2
"Very bad"	3

Component 1 score: _____

Component 2: Sleep latency

1. Examine question #2, and assign scores as follows:

Respo\nse	Score
≤15 minutes	0
16-30 minutes	1
31-60 minutes	2
> 60 minutes	3

Question #2 score: _____

2. Examine question #5a, and assign scores as follows:

Response	Score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Question #5a score: _____

3. Add #2 score and #5a score

Sum of #2 and #5a: _____

4. Assign component 2 score as follows:

Sum of #2 and #5a	Component 2 score
0	0
1-2	1
3-4	2
5-6	3

Component 2 score: _____

Component 3: Sleep duration

Examine question #4, and assign scores as follows:

Response	Component 3 score
> 7 hours	0
6-7 hours	1
5-6 hours	2
< 5 hours	3

Component 3 score: _____

Component 4: Habitual sleep efficiency

1. Write the number of hours slept (question #4) here: _____

2. Calculate the number of hours spent in bed:

   Getting up time (question #3): _____

   Bedtime (question #1): _____

   _____

   Number of hours spent in bed: _____

3. Calculate habitual sleep efficiency as follows:

   (Number of hours slept/Number of hours spent in bed) X 100 = Habitual sleep efficiency (%)

   (_____/_____) X 100 = %

4. Assign component 4 score as follows:

Habitual sleep efficiency %	Component 4 score
> 85%	0
75-84%	1
65-74%	2
< 65%	3

Component 4 score: _____

Component 5: Step disturbances

1. Examine questions #5b-5j, and assign scores for each question as follows:

Response	Score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

5b score: _____

5c score: _____

5d score: _____

5e score: _____

5f score: _____

5g score: _____

5h score: _____

5i score: _____

5j score: _____

2. Add the scores for questions #5b-5j:

Sum of #5b-5j: _____

3. Assign component 5 score as follows:

Sum of #5b-5j	Component 5 score
0	0
1-9	1
10-18-4	2
19-27	3

Component 5 score: _____

Component 6: Use of sleeping medication

Examine question #7 and assign scores as follows:

Response	Component 6 score
Not during the past month	0
Less than once a week	1
Once or twice a week	2
Three or more times a week	3

Component 6 score: _____

Component 7: Daytime dysfunction

1. Examine question #8, and assign scores as follows:

Response	Score
Never	0
Once or twice	1
Once or twice each week	2
Three or more times each week	3

Question#8 score: _____

2. Examine question #9, and assign scores as follows:

Response	Score
No problem at all	0
Only a very slight problem	1
Somewhat of a problem	2
A very big problem	3

Question #9 score: _____

3. Add the scores for question #8 and #9:

Sum of #8 and #9: _____

4. Assign component 7 score as follows:

Sum of #8 and #9	Component 7 score
0	0
1-2	1
3-4	2
5-6	3

Component 7 score: _____

Global PSQI Score

Add the seven component scores together:

Global PSQI Score: _____

Hospital Anxiety and Depression Scale (HADS)

Please answer the following questions about how you are feeling currently. Choose one response from the four given for each question. Try to give an immediate response and avoid thinking too long about your answers.

A	**I feel tense or 'wound up':**	
	Most of the time	3
	A lot of the time	2
	From time to time, occasionally	1
	Not at all	0

D	**I still enjoy the things I used to enjoy:**	
	Definitely as much	0
	Not quite so much	1
	Only a little	2
	Hardly at all	3

A	**I get a sort of frightened feeling as if something awful is about to happen:**	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0

D	**I can laugh and see the funny side of things:**	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3

A	**Worrying thoughts go through my mind:**	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not	1

	too often	
	Only occasionally	0

D	**I feel cheerful:**	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0

A	**I can sit at ease and feel relaxed:**	
	Definitely	0
	Usually	1
	Not Often	2
	Not at all	3

D	**I feel as if I am slowed down:**	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0

A	**I get a sort of frightened feeling like 'butterflies' in the stomach:**	
	Not at all	0
	Occasionally	1
	Quite Often	2
	Very Often	3

D	**I have lost interest in my appearance:**	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care as ever	0

A	**I feel restless as I have to be on the move:**	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0

D	**I look forward with enjoyment to things:**	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3

A	**I get sudden feelings of panic:**	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0

D	**I can enjoy a good book or radio or TV program:**	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

	Scoring (add the As = Anxiety. Add the Ds = Depression). The norms below will give you an idea of the level of Anxiety and Depression.	
	0-7 = Normal	
	8-10 = Borderline abnormal	
	11-21 = Abnormal	

Reference:

Zigmond and Snaith (1983)

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

Dear XXXX

Thank you for choosing to take part in the TIME study.

We are interested in potential ways that that taking your blood pressure medication at a certain time of day could affect your health and wellbeing.

One of the aspects that could be affected, positively or negatively, is sleep. We would like to invite you to take part in a questionnaire-based sub-study of TIME that will look at whether your sleep is affected by the time of dosage that you have been randomly allocated for the TIME study.

If you are interested in finding out more about this sleep quality sub-study, please click on the following link:

XXXXXXX

Your choice about whether to take part in this sub-study does not affect your participation in the main TIME study.

Thank you for your consideration,

The TIME study team

TIME Sleep Quality Sub-study: Informed Consent Form

(Standard yes/no tick box format)

I confirm that I have read and understood the *information sheet* for the above sub-study. I have had the opportunity to consider the information and ask questions, and have had these answered satisfactorily. Y/N

I understand that I will be sent emails asking me to complete an online questionnaire about sleep quality. Y/N

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. If I withdraw I understand that the sponsor will retain the data collected up to the point I withdraw. Y/N

I agree to take part in the TIME Sleep Quality Sub-study Y/N

Please enter your name to confirm that you have read the information sheet and answered the questions above. By entering the following information this will be equivalent to your signature on this consent form.

Forename _____ **Surname** _____

I have read, answered and understood all of the above questions and understand this is an electronic signature ☐

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	x
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,3
	5b	Name and contact information for the trial sponsor	3
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	x
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	3
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_______5_______
	6b	Explanation for choice of comparators	_______n/a_______
Objectives	7	Specific objectives or hypotheses	_______5_______
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_______5_______
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	________n/a_______
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_________5_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	________6_______
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	________n/a_______
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	________n/a_______
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	________6_______
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____7-8_________
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____6_________
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_______9_______
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_________6_____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4, 7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	n/a
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	x
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	8
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that	14

		limit such access for investigators	
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__n/a_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___11_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__n/a_____ __
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset and statistical code	___14_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___Y_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____n/a_____ __

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.