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Treatment in morning versus evening study

Submission date 21/08/2014	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol [X] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 20/10/2014	**Overall study status** Completed	
Last Edited 13/10/2022	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
Treatment in Morning versus Evening (TIME) is a study to compare the treatment for high blood pressure using hypertensive drugs given in the evening with the usual morning medication. This is done using an online system to record any side effects or changes due to the change in their medication. This automated system has worked well in our initial phase of this study with good patient response. Record-linkage to hospitalisations and deaths will be carried out and events monitored. Heart attack, stroke or death will be recorded and analysed to see if the timing of the medication has any impact.

Who can participate?
People who are already taking antihypertensive medication in usual care

What does the study involve?
Participants take part by registering on a secure, study-specific website. Those who are eligible are randomly allocated to continue taking medication at their usual time (usually morning) or to switch to taking medication in the evening. Participants receive regular emails with simple links to record responses to track progress. Participants, people on their behalf, or GPs can record any side effects at any time online. Participants are followed up for 4 years.

What are the possible benefits and risks of participating?
Taking hypertensive medication in the evening may reduce the number of heart attack or stroke compared with usual morning dosing, and so is potentially of benefit to all hypertensive patients in the future. There are no known risks for patients taking part in the study.

Where is the study run from?
The study is sponsored by the University of Dundee, UK and run from the Medicines Monitoring Unit (MEMO) within this. The study is internet based and participants can be recruited from across the UK. They will be recruited from general practices, hospitals or by social media.

When is the study starting and how long is it expected to run for?
August 2011 to July 2022

Who is funding the study?
British Heart Foundation (UK)

Who is the main contact?
Ms Wendy Saywood
wendys@memo.dundee.ac.uk

Study website
https://www.timestudy.co.uk/

Contact information

Type(s)
Scientific

Contact name
Dr Rebecca Barr

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
17071

Study information

Scientific Title
Treatment In Morning versus Evening: an observational study

Acronym
TIME

Study objectives
A trial comparing evening dosing of usual antihypertensive therapy with conventional morning dose is proposed.

Ethics approval required
Old ethics approval format

Ethics approval(s)
East of Scotland Research Ethics Service (EoSRES) REC 1; 28/05/2011 (approval for the pilot study), 26/05/2014 (approval to move on to full study); ref. 11/AL/0309

Study design
Randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
https://www.timestudy.co.uk/info_sheets/TIME%20STUDY%20-%20Patient%20Information%20Sheet.pdf

Health condition(s) or problem(s) studied
Topic: Primary Care, Cardiovascular disease; Subtopic: Other Primary Care, Cardiovascular (all Subtopics); Disease: All Diseases, Other

Interventions
Timing of medication switch: Subjects already taking hypertensive medication in usual care will be identified from collaborating practices and within secondary care clinics. Subjects will be invited to participate in the study by registering on a study website. Registered subjects who meet the inclusion criteria will be randomised to continue taking medicine at their usual time (most often in the morning) or to switch to taking medication in the evening (or morning if evening is their usual time).

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
The Anti Platelet Trialists' Collaboration: composite endpoint of non-fatal myocardial infarction, non-fatal stroke or vascular death.

Secondary outcome measures

1. Each component of the primary endpoint
2. Hospitalisation for non-fatal stroke
3. Hospitalisation for non-fatal MI
4. Vascular death
5. All-cause mortality
6. Hospitalisation or death from congestive heart failure.

1. Adherence to the evening dosing regimen vs morning (patient reported) with particular reference to patients taking diuretic therapy.
2. Patient reported and hospitalised adverse events in the morning versus evening groups will be compared. In particular falls and fractures will be recorded.
3. Home BP readings taken by a subset of patients will be compared between morning & evening dosing.
4. An additional proposed substudy is a telephone administered cognitive function assessment to compare patients on morning and evening dosing.

Overall study start date
03/08/2011

Completion date
27/07/2022

Eligibility

Key inclusion criteria
1. Both diagnosed and treated for hypertension (all forms) with at least one antihypertensive drug
2. Aged above 18 years
3. Have a valid email address

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Proposed following AM09: >20,000; Actual number recruited to date: 20,860 (AM09 (REC ref AM11): Approved 22/12/2015)

Total final enrolment
21104

Key exclusion criteria

1. Subjects who take twice daily antihypertensive therapy.
2. Subjects who work shift patterns that include a night shift.
3. Subjects who unwilling to consent to:
3.1. Follow up
3.2. Provide a surrogate to be contacted and/or
3.3. Give consent for their family practice to release follow up clinical data
3.4. To have their physical case records abstracted if required
3.5. To have their electronic case records searched and abstracted if required
3.6. To allow their consent from to be copied to authorities from whom the study team is requesting medical data
4. Those participating in another clinical trial or who have done in the last 3 months

Date of first enrolment
07/12/2011

Date of final enrolment
05/06/2018

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre
Ninewells Hospital and Medical School
Dundee
United Kingdom
DD1 9SY

Sponsor information

Organisation
NHS Tayside (UK)

Sponsor details
R&D Office
Level 9
Ninewells Hospital and Medical School
Ninewells Avenue
Dundee
Scotland
United Kingdom
DD1 9SY

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/000ywep40

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation (BHF) (UK); Grant Codes: CS/14/1/30659

Alternative Name(s)
the_bhf, The British Heart Foundation, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Presentation of results at European Society of Cardiology (ESC) Congress (Barcelona 26-29 August 2022) and ISH (Kyoto, 12-16 October 2022)
Substudies will be published separately.
Results have been shared by email with all participants and participating research networks (see attached lay summary).

Intention to publish date
12/10/2022

Individual participant data (IPD) sharing plan
Access to a de-identified participant dataset and data dictionary is available upon reasonable request to researchers who provide a methodologically sound proposal, with no prespecified restrictions on data use. Any such requests should be sent to the corresponding author for consideration by the trial steering committee. There might be restrictions on sharing data

derived from record-linkage to NHS datasets. A period of 18 months after publication of the main study results should elapse before requests are made, to allow the authors to publish substudies and further analyses.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	09/02/2016		Yes	No
Protocol article	substudy protocol	07/06/2018		Yes	No
Other publications	analysis of recruitment, retention and follow-up rates	01/12/2017	18/03/2020	Yes	No
Statistical Analysis Plan	version 1	29/06/2022	29/07/2022	No	No
Plain English results	version 1.0	11/10/2022	13/10/2022	No	Yes
Results article		11/10/2022	13/10/2022	Yes	No