Patient Information Sheet

Principal Investigator: Professor Tom MacDonald

Contact for queries:
If you have any queries about this study, you can contact: Professor Tom MacDonald. Dr Isla Mackenzie (Doctor), Evelyn Findlay (Study Co-ordinator) or one of the other study doctors or nurses at the Medicines Monitoring Unit (MEMO), University of Dundee on 01382 383119 or Freephone 0800 9173509(answering machine out of office hours).
Email:- info@timestudy.co.uk

Study title: **Treatment In Morning versus Evening (TIME)Study**

We invite you to participate in a research project. We believe it to be of potential importance. However, before you decide whether or not you wish to participate, we need to be sure that you understand firstly why we are doing it, and secondly what it would involve if you agree. We are therefore providing you with the following information. Read it carefully and be sure to ask any questions you have, and, if you want, discuss it with outsiders. We will do our best to explain and to provide any further information you may ask now or later. You do not have to make an immediate decision.

Why are we doing this study?
Patients traditionally take their blood pressure lowering tablets in the morning and blood pressure is traditionally measured at some time during the working day. Most of the current evidence that shows the benefits to patients of reducing their blood pressure comes from studies where tablets were taken in the morning and BP was measured in the daytime.

In recent years, special monitors that can measure blood pressure throughout the day and the night have been developed. Results from studies using these monitors have suggested that night time blood pressure might be a better measurement of the benefits of blood pressure lowering. In addition, tablets taken at night lower night-time blood pressure more than tablets taken in the morning. The big question is, would night time dosing be better (or worse) than morning dosing in preventing the bad things associated with high blood pressure (such as strokes and heart attacks)?

The present study will try to answer this question. To do this we are asking patients who take medicines for high blood pressure to take part in a study that will compare morning dosing (some time between 6am and 10am) with night-time dosing (some time between 8pm and midnight).

Why are we doing this study in this way?
To be able to answer this question we will need to study a lot of people. The reason for this is that heart attacks and stroke events are uncommon. To be able to know with confidence that morning and night-time dosing are different (or the same) at preventing these events, a lot of

people have to be studied over a number of years. For practical (and cost) reasons such a study cannot really be done in the conventional way where patients see a clinician regularly for a large number of study visits. For this reason we are doing this study by email and a secure website so there are no study visits at all. However, this means that only those patients who have internet access at home and a valid email address that we can use to regularly contact them, can participate. If you do not have this in your home then I am afraid that you cannot participate.

Who else cannot take part in this research?
The following people will not be able to participate:

Those who currently take blood pressure lowering tablets both in the morning and at night.
Those who work night shifts.
Those participating in another clinical trial or who have done in the last 3 months.

What do I do if I am interested in taking part in this study?
If you have email facilities and you would like to participate in this study you can register your interest by going to https://www.timestudy.co.uk Note that this is a secure website like the banks use.

After you register your interest you will be sent an email with a web-link to confirm your email address.

Consent
We will want to be sure that you understand all of the things that the study needs to be successful and we will need you to explicitly consent to each of these. This is so that we have a positive record that you agree to each of these things.

For this reason, you will be asked to tick boxes agreeing to each of the things required to make the study a success. These are explained below:

What will I have to do if I do take part?
The way this trial works is that people who sign up to it will be followed over time to see if they have to go to hospital with a heart attack or stroke or if, unfortunately, they pass away due to a cardiovascular problem. This follow up is possible because the NHS keeps central records of all hospital admissions and the General Registers Office (Scotland), the Office for National Statistics (England), and the Government in Wales keep a record of all causes of death. We can only get these data about you with your explicit consent, so to take part in this trial you have to agree that these agencies can let us know that one of these things has happened to you.

To do this, we have to share some of your personal data (name, date of birth, address/postcode, NHS/CHI number and possibly GP address) with the relevant NHS or Government agency. These are:

- Health and Social Care Information Centre (HSCIC) and Office for National Statistics (ONS) in England,
- The NHS National Services Scotland and the General Register Office in Scotland,
- The NHS Shared Services Partnership in Wales
- The NHS Health and social Care in Northern Ireland(HSC).

These agencies will look at your electronic medical records, and then let us know about any hospitalisations, occurrences of cancer, or death. Please note that, apart from these agencies, your information will not be shared with anyone not involved with the TIME Study or your NHS care. If you want more information then please contact a member of the study team.

(Note: that if a stroke or heart attack does happen to you, you can report it to us yourself on the web-site. This is particularly useful where this event occurs outside of the UK as we will only be able to track events in the UK).

Since we will study large numbers of patients over a number of years it is (unfortunately) inevitable that some people will die and some will become unwell in other ways that make it difficult for them to keep in contact with us. We can never predict who this will happen to. In order to be able to be certain about what happened to these patients we are asking all participants to let medical researchers look at their electronic or paper health records. It would also be helpful if you were able to provide the contact details of a close relative or friend that we could contact if we were unable to contact you for any reason. Finally, we would like to be able to contact your family doctors to help find out what has happened to you.

We wish to keep in periodic contact with you. We will do this by sending you emails, initially at 1 month and subsequently 3 or 6 monthly intervals. These emails will contain web-links to enable the vast majority of people to quickly answer our questions. For example, the email may ask:

Are you still taking your medicines in the morning / at night? If you are still taking your treatment at this time and there have been no changes to your prescribed treatment and there is nothing you want to tell us then please click this link (example link https//www.timestudy.co.uk/Ab1433296553).

This is all you have to do if there is no change to your information. You will then get taken to a web page thanking you for your response.

If you wish to tell us that something has changed then you will be asked to click another link: (example link https//www.timestudy.co.uk/Axyzt433865). This will take you to the website page where you can enter the information you want to tell us. You will then get shown a web page thanking you for your response.

Details about you collected at baseline

You will be asked to fill in contact details about yourself. This is to allow us to be able to contact you by telephone or letter if, for some reason, your email stops working.

We would also like details of an alternative person we could contact should you stop replying to us for any reason. This could be a close family member for example. Finally, we will need your agreement to be able to contact your family doctor to find out about your health if required.

We need to know about your own history of high blood pressure, your drug treatment, a family history, whether you have other significant medical conditions etc. This sounds like a lot but nearly all of it is tick boxes or picking from a list of options. You should not worry if

you cannot remember precise details as most people cannot. You can always go back later and edit your data if you wish.

Randomisation
When you have done this, you will then be allocated to take your treatment in the morning or at night. This will be allocated to you at random by a computer and cannot then be changed so if you would be unhappy to take your medicines at night then you should not participate. You will also be unable to participate if you take twice daily medication for blood pressure or if you work night shifts.

When we do not know which way of treating patients is best, we need to make a comparison. An important part of making a *fair comparison* is 'randomisation'. Most large trials are randomised. The decision about which treatment you receive is random – based on chance. This is done by a computer programme, not the patient or the doctor. This is called randomisation. Randomisation ensures that the two groups of people in the trial are as similar as possible. This means that the results are more reliable and it is the best way of ensuring that the results of the trial are not biased by the way treatments are allocated.

Are there any possible problems that could arise if I participate?
Part of the reason for doing the study is to see if there are any downsides to taking tablets in the morning compared with at night time. Some of the possible issues that we speculate might arise are mainly to do with evening dosing. We would like to know if these are problems or not.

Diuretic therapy (with thiazide-type diuretics) and evening dosing
Diuretic tablets (sometimes known as 'water tablets' i.e. bendroflumethiazide) could theoretically increase urine volume at night and lead to early wakening to visit the toilet. In practice, when people have been on these tablets for a long time the effect on urine volume is small or absent. However, we recognise that this might still be a problem. For those people taking this sort of tablet we would like patients to try taking this tablet in the evening but if they find it a problem they could take it earlier (6pm). If this still does not resolve the problem then they could take it at 4pm and so on in 2 hour increments until it is no longer a problem. We would like patients to tell us about this as we need to know if this really is an issue or not.

Diuretic therapy (with loop-type diuretics) and evening dosing
A few patients will be taking so-called loop diuretics like frusemide or bumetanide. These tablets typically cause a prompt increase in urine volume that lasts a few hours. Patients taking these tablets will be aware of how long this effect lasts in them. We would like patients taking these drugs who are randomly allocated evening dosing to take these tablets at 6pm in the first instance. If this results in difficulties then patients should revert to taking this tablet in the morning. Again, these practical issues are part of the reason for doing the research and we want to collect these data.

Evening dosing and nocturnal dizziness or morning dizziness
Some patients, often older men, get up at night to visit the toilet or for other reasons. We want to know if taking medicines in the evening causes increased symptoms of dizziness or light headedness when they get up at night or first thing in the morning. We would like to know if such symptoms are an issue.

Other Commonly asked Questions

What if I sign up but then change my mind?
As with all research you are free at any time to withdraw without giving a reason. Your medical care and legal rights will not be affected by this. With this particular trial this can be done by going to the website to register your withdrawal. You can withdraw partially or completely. Partial withdrawal means that you no longer want to take treatment at the allocated time but that you do not mind being followed up by the study team. Full withdrawal means that you do not wish to be followed up any more.

Who will see my personal data?
As well as the agencies already named, clinical staff running the study may see your personal health records but they will treat these in strict confidence. Your study files that undergo statistical analysis by non-clinical staff will be anonymised. Publications will never contain any personal or identifiable details about you. Nowadays all studies are monitored and audited by the study sponsor (University of Dundee-NHS Tayside) or by external government agencies such as the Medicines and Healthcare products Regulatory Agency (MHRA). Monitors and auditors work under conditions of strict confidentiality. Your data will be kept in a secure location at the University of Dundee-NHS Tayside for 5 years after the study has completed in line with European Guidelines.

What if there is a problem?
If you have a concern about any aspect of this study you should ask to speak with the study doctor who will do their best to answer your questions [tel. 01382 383119]. If you remain unhappy and wish to complain formally you can do this through the Complaints Procedure of your GP's practice. Details can be obtained from the practice.
In the event that something goes wrong and you are harmed during the research study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation against either the University of Dundee or your GP practice.

Can I get further information?
The study website contains much more information including details of those involved with the research and frequently asked questions. We also have a telephone help-line for issues not covered by the website – 0800 917 3509

Who will approve this trial?
The East of Scotland Research Ethics Service (EoSRES), which has the responsibility for scrutinising all proposals for medical research on humans, has examined the proposal and has raised no objections from the point of view of medical ethics. EoSRES will evaluate and monitor ethical issues as the trial proceeds. It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from NHS Tayside, whose role it is to check that research is properly conducted and the interests of those taking part are adequately protected.

The trial has undergone scientific scrutiny by doctors and scientists belonging to the British Hypertension Society. The trial has now completed a successful pilot phase and the roll-out has now been funded by the British Heart Foundation.

Will my doctor know if I am participating?
We are unable to inform all GPs of their patient participation in the study, but advise patients to update their GP at their next visit.

What if I am taking part in another study?
If you are taking part in another study that is a clinical trial you cannot participate in this one as well. If you are unsure about this, please contact us to check. If you have recently completed another clinical trial you must wait 3 months from the end of that study before signing up to this one.

Will the results of this study be made public?
Yes we will publish the results of this study as soon as they are available. We will also email the results to all participants.

Thank you for taking the time to read this Information Sheet and for considering taking part in this study.