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**STUDY OF PATIENTS WITH SEVERE HYPERTENSION REFERRED TO HOSPITAL FOR SAME DAY SPECIALIST REVIEW**

 **Final Version 1.0**

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**Short title:** *Severe Hypertension*

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**Study Sponsor:** University of Nottingham

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 Professor Ian Hall NIHR Senior Investigator award

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# STUDY SYNOPSIS

|  |  |
| --- | --- |
| Title | Study of patients with severe hypertension referred to hospital for same day specialist review |
| Acronym |  |
| Chief Investigator | Dr Mark Glover |
| Study centre(s) | Nottingham University Hospitals NHS Trust |
| Objectives | To establish the characteristics and natural history of severe hypertension in adults referred for same day review in comparison with asymptomatic severe hypertension |
| Number of participants / tissue samples  | 300 Cases, 300 Controls |
| Diagnosis and main criteria for inclusion | Inclusion Criteria:-Adults aged 18 and over- Severe Hypertension (Systolic >180mmHg and/or Diastolic >120mmHg) - Referred for same day specialist review (for cases only)Exclusion Criteria:* Pre-existing Renal Replacement Therapy
* Acute Stroke
 |
| Duration of study | Planned start date August 2020 with planned project duration 18 years |
| Description of interventions | Two venepuncturesTwo spot urine samplesTwo 24 hour urine collections (exceptionally an extra 24 hour urine collection for metanephrines will be requested if not performed clinically) |
| Statistical methods | Association testing only |

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# ABBREVIATIONS

NUH : Nottingham University Hospitals

# STUDY BACKGROUND INFORMATION AND RATIONALE

**Introduction**

Hypertension is defined as a clinic blood pressure ≥140/90mmHg and home or ambulatory blood pressure of ≥ 135/85mmHg. Severe hypertension however is defined as a clinic systolic blood pressure ≥ 180mmHg and/or a diastolic blood pressure ≥ 120mgHg (1) . ‘Hypertensive emergencies’ is an umbrella term referring to the presence of severe hypertension (as defined above) plus evidence of impending or progressive organ damage. This includes accelerated/malignant hypertension (severe hypertension and grade 3 or 4 hypertensive retinopathy). It also includes other complications of hypertension such as acute deterioration in renal function, hypertensive encephalopathy, cerebral infarction or haemorrhage, acute pulmonary oedema, acute coronary syndrome, aortic dissection and eclampsia. Causes of secondary hypertension requiring urgent medical attention such as a phaeochromocytoma crisis is also considered a hypertensive emergency.

Isolated severe hypertension with no evidence of acute organ damage is sometimes termed asymptomatic severe hypertension. Another term used in published literature is ‘Hypertensive Urgencies’, however there appears to be discrepancies in what this term is used to mean. In some studies ‘hypertensive urgencies’ has been used to describe individuals with isolated severe hypertension without any evidence of acute organ damage (2). However, the term ‘hypertensive urgencies’ has also been used to describe severe hypertension with acute organ distress (3). For this reason we will avoid the use of the term hypertensive urgencies’.

NICE guidance states that individuals with severe hypertension only require same day specialist review when there is evidence of a hypertensive emergency indicating impending or progressive end organ damage. (1) This would appear to differ from previous practice as in published literature up to a quarter of patients admitted with severe hypertension have no evidence of organ dysfunction (2).

The aim of this project is to establish the natural history of patients referred for same day specialist review of their severe hypertension in comparison with individuals with the same degree of uncontrolled hypertension but no features warranting referral for same day review. At present there a lack of evidence suggesting what factors indicate the need for same day specialist review. Considering the prevalence of hypertension within the general population, hypertensive emergencies occur in a minority. However, in light of the presence or threat of end organ damage and the increased mortality (4) seen in this cohort of patients it is necessary that cases are identified and reviewed in specialist care promptly. Conversely, with uncontrolled hypertension being a common finding in general practice, it would not be feasible in practical or cost-effective to review every patient with uncontrolled hypertension in specialist care on a same-day basis and thus there is also a financial benefit to the NHS in establishing who will most benefit from same day review.

**Epidemiology**

Hypertension is common with an estimated prevalence of 44% in European countries. (5). Hypertension is also a worldwide burden with an estimated 1 in 4 people worldwide (6). Hypertension is of significance due to it being a major cardiovascular disease risk factor which in turn is a leading cause of death in the developed world. Hypertensive emergencies, including malignant phase or accelerated hypertension represent a minority of the overall burden of hypertension however are associated with the poorest outcomes.

Despite availability of effective and affordable anti-hypertensive and evidence based guidelines on the management of hypertension in primary care, the incidence of malignant hypertension has remained static over the last 40 years (7) and the incidence of uncontrolled hypertension presenting to the emergency department is increasing (8).

Numerous studies have discussed potential risk factors for hypertensive emergencies including ethnicity, age, gender and severity of pre-existing hypertension. Whilst previous studies have stated the ethnicity distribution amongst participants, it is not possible to draw any conclusions on the role of ethnicity in the development of malignant hypertension as information on the ethnic make-up of the population studied is often not included (2). The STAT registry collated data on 1588 consecutive patients with acute severe hypertension and revealed a median age of 58 years, 56% of cases were black and 49% women (9). However, there is considerable variability in mean age of presentation and gender distribution (4) (2) across different studies. A retrospective study involving 670 patents found 70% on patients with hypertensive emergencies were already on antihypertensive drugs (2) however a different study specifically looking at malignant hypertension showed only 25% of patients were taking antihypertensive drugs at presentation (7).

**Pathophysiology**

For the majority of patients diagnosed with hypertension an underlying cause for their raised blood pressure is not established. Only around 5% of individuals are confirmed to have a diagnosis responsible for secondary hypertension such as underlying renal disease or an endocrine diagnosis such as Cushing’s syndrome or hyperaldosteronism. For the remainder of patients with primary or ‘Essential’ hypertension, pathophysiology is poorly understood. There are a number of possible risk factors predisposing an individual to development of hypertension including advancing age, increased BMI, Black race, family history of hypertension, high sodium diet, alcohol excess and lack of physical activity.

A number of mechanisms have been suggested in attempts to explain the pathophysiology of primary hypertension however many questions remain unanswered making research in this area a high priority. It has long been established that blood pressure is determined by cardiac output and systemic vascular resistance and therefore the pathogenesis of hypertension must involve an increase in either or both. Multiple possible mechanisms by which this occurs have been implicated and include disturbances of the renin-aldosterone pathway, action of the autonomic nervous system, endothelial dysfunction and the action of vasoactive substances (10). It is likely however that essential hypertension is the result of complex interplay between multiple physiological mechanisms and environmental factors rather than any one cause in isolation.

Hypertension is more likely if an individual has a family history of hypertension in one or both parents suggesting a possible genetic component to its pathophysiology. Whilst there is the obvious source of confounding with close familial members tending to have a similar lifestyle, it is estimated that genetic factors are responsible for 30% of the variation in blood pressure in various populations (10). Whilst there are examples of single mutation causes of hypertension such as Liddle’s or Gordon’s syndrome, these conditions are exceedingly rare and do not play a role in the vast majority of individuals with hypertension.

The relationship between severe hypertension and organ dysfunction is complex and not fully understood. Severe hypertension can certainly lead to renal, neurological, cardiac dysfunction however it is also possible for a primary organ dysfunction such as renal failure to result in secondary severe hypertension. Possible mechanisms of organ dysfunction in severe hypertension include hypercoagulability, pressure effects of an increased haemodynamic load, sympathetic nervous system activation and catecholamine release, activation of the renin-aldosterone pathway. Environmental factors such as salt consumption and obesity in addition to differences in age, sex and ethnicity are all thought to have a role in the risk of developing end organ damage in the presence of severe hypertension (11).

One study assessing cardiovascular risk and mortality in malignant hypertension found individuals with malignant hypertension had fewer cardiovascular risk factors such as obesity or diabetes compared with hypertensive controls however had an increased incidence of cardiovascular death and worse renal outcomes. This raises the possibility that there may be a different underlying mechanism in some individuals.

**Prognosis**

Prior to the introduction of effective anti-hypertensive drugs, survival rates in malignant hypertension were very poor. The term ‘malignant hypertension’ was coined because one year survival rates as low as 10% were similar to that of disseminated malignancy (12) with most deaths occurring in the first year post diagnosis (13). With the introduction of effective pharmacological agents to control blood pressure in the 1950s-1960s, survival rates began to improve (14).

From as early as 1970 however there has been documented evidence of a patient group with acute severe hypertension who continue to progress rapidly despite anti-hypertensive agents. Clinical course for these patients is often complicated by development of renal failure, congestive heart failure and/or encephalopathy (13). For patients with primary malignant hypertension that failed to respond to initial pharmacological treatment, average survival was found to be as low as 8.8 months (13).

A retrospective case control study in 1985 compared the mortality of malignant hypertension with age and sex matched controls diagnosed with ‘benign’ hypertension. Despite very similar degrees of blood pressure control (mean of 177/107 in malignant hypertension group and 172/101 in benign hypertension group) those with malignant hypertension were almost twice as likely to die in the 10 year follow up period largely from renal and cardiovascular events (15).

Whilst there have been improvements in the mortality rate of severe hypertension and malignant hypertension (7), there is still considerable risk of morbidity and death associated with hypertensive emergencies. This has been demonstrated both in the short term with a 90 day mortality rate of 11% for hypertensive emergencies compared with 0.3% for severe hypertension and longer term with a mortality rate quoted between 12% (16) and 38.9% (2) at 1 year.

**Summary**

Hypertension is a common cause of cardiovascular disease which in turn is a leading cause of death in the UK. Severe hypertension is often asymptomatic however can present with rapidly developing end organ damage such as acute kidney injury or cardiac failure. NICE guidance states that patients with severe hypertension and emergency features require same day specialist review. However, there is to date no study data comparing the natural history of patients with severe hypertension and emergency features reviewed on a same day basis with individuals with isolated severe hypertension in the outpatient clinic. This project aims to address this important area where there is an absence of an evidence base and seeks to address the research recommendation in the 2019 NICE hypertension guideline NG136 which calls for such clinical data to be gathered.

# STUDY OBJECTIVES AND PURPOSE

## PURPOSE

The purpose of the study is to establish the characteristics and natural history of adults with severe hypertension who are referred for same day specialist review in comparison with adults with a similar level of severe hypertension referred for review in an outpatient setting.

## PRIMARY OBJECTIVE

To identify the natural history of adults with severe hypertension presenting for same day specialist review in comparison with adults with similar level of severe hypertension who have not required same day review.

## SECONDARY OBJECTIVES

To characterise the plasma and urine electrolyte and hormone profiles of adults with accelerated hypertension compared to asymptomatic severely hypertensive controls

To characterise the urinary sodium transporter profile in patients with accelerated Hypertension and asymptomatic severe hypertension

# STUDY DESIGN

## STUDY CONFIGURATION

The study shall be managed from the University of Nottingham and shall recruit from Nottingham University Hospitals NHS Trust

We propose to conduct a prospective case-control study in order to establish the natural history of individuals presenting with severe hypertension requiring same day review with a control group consisting of individuals with similar levels of uncontrolled hypertension who have not required same day assessment in secondary care. We shall also characterise the phenotype of acute severe hypertension by measurement of plasma and urine electrolytes, hormonal profiles and abundance of sodium transporters in the urine in patients and controls.

### Primary endpoint

Collation of data including diagnosis, past medical history, drug history, relevant investigation results and outcome for adults with severe hypertension

### Secondary endpoint

To characterise the plasma and urine electrolyte and hormone profiles of adults with accelerated hypertension compared to asymptomatic severely hypertensive controls

To characterise the urinary exosomal sodium transporter profile in patients with accelerated hypertension and asymptomatic severe hypertension

## STUDY MANAGEMENT

The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

## DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

**STUDY DURATION**

Planned start date August 2020 with planned project duration 18 years

PARTICIPANT DURATION

Participants will be enrolled in the study for a period of 10 years however will usually only require interaction with the research team at the time of recruitment and at a convalescent visit at 3 months post recruitment. Further review at 1 year, 2 years, 5 years and 10 years will be via review of electronic records. Exceptionally, if blood pressure and outcome data not available via electronic records we will request a review in person in the outpatient clinic.

### End of the Study

The end of the study will be the last ‘10 year review’ of the last participant.

## SELECTION AND WITHDRAWAL OF STUDY PARTICIPANTS

### Recruitment

Participants will be recruited from General Medicine admissions areas and inpatient wards at Nottingham University Hospitals (NUH). Participants in the control arm will be recruited from Hypertension Clinic or primary care. The initial approach will be from a member of the patient’s usual care team.

The investigator or their nominee, e.g. from the research team or a member of the participant’s usual care team, will inform the participant of all aspects pertaining to participation in the study.

If needed, the usual NHS hospital interpreter and translator services will be available to assist with discussion of the trial, the participant information sheets, and consent forms, but the consent forms and information sheets will not be available printed in other languages.

It will be explained to the potential participant that that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate. Remaining tissue samples can be destroyed if the participant so wishes.

### Eligibility criteria

### Inclusion criteria

Inclusion Criteria:

-Adults aged 18 -100

- Severe Hypertension (Systolic >180mmHg and/or Diastolic >120mmHg)

- Referred for same day specialist review (for cases only)

- Able to give informed consent

### Exclusion criteria

Exclusion Criteria:

* Pre-existing Renal Replacement Therapy
* Acute Stroke

### Informed consent

All participants will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the trial. The Investigator will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

Informed consent will be collected from each participant before they undergo any interventions related to the study. Consent will be taken by the Principle Investigator or a designated member of their research team with appropriate skills and experience. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient’s hospital records.

Should there be any subsequent amendment to the final protocol, which might affect a participant’s participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

## STUDY TREATMENT AND REGIMEN

Potential case participants will be identified by clinicians providing same-day review in the context of severe hypertension within Acute Medicine. Control participants will be identified by the responsible clinician in outpatient hypertension clinics. . The Principle Investigator or a designated member of the research team will then discuss the study with potential participants and after reading the patient information sheet and having time to ask questions the participant will be asked to sign a consent form if they wish to participate. Once consent has been obtained the principle investigator or designated member of the research team will review the participant’s medical record to ensure eligibility criteria met. If eligibility criteria met the study team will document the participant’s medical background and medication history.

At the same visit a single venous blood sample (33 ml blood) will be taken by a doctor, nurse or phlebotomist who is fully trained with extensive experience in this technique according to standard methods used in routine clinical care within the NHS. The person who performs the venepuncture shall hold a substantive or honorary contract with the NHS and perform venepuncture as a routine part of their clinical work. A spot urine sample of up to 100ml will be taken during the initial visit. A 24 hour urine collection for urinary electrolytes will be performed. 24 Hour Urine collections can be returned to NUH Pathology if participants remain in hospital. For outpatients, 24 hour urine collections can be returned to participants GP surgery if located within Nottinghamshire or returned to NUH pathology otherwise. A second 24 hour urine collection for metanephrines will be requested if not already carried out however this forms part of usual care of an individual presenting with severe hypertension.

Participants will be invited to attend a follow-up visit at 3 months at which point a second single 25 ml blood sample and spot urine sample of up to 100ml shall be taken. Participants will also be asked to repeat the 24 hour urine collection at this point.

The blood test may be mildly uncomfortable and sometimes results in a small bruise which shall be minimised by the application of pressure at the site of venepuncture as per standard clinical practise in the NHS. Where possible, as these patients will be undergoing venepuncture as part of their normal clinical care, we shall offer to collect blood at the same time as their next clinical sample if desired by the patient.

One year after recruitment, providing participants have given their explicit consent, we will review their electronic health records to record data relating to their recorded blood pressure and hypertension related outcomes. If we are unable to obtain this information from electronic health records we will contact participant’s General Practitioner. Participants will not need to be present at the time of the one year review unless we are unable to obtain relevant information electronically or via their GP in which case we will request review in an outpatient clinic. The same process will be repeated at 2 years, 5 years and 10 years.

### Sample size and justification

We aim to recruit 300 cases and 300 controls. This sample size has been determined by frequency of presentation of patients with severe hypertension and sample sizes of previous studies of malignant hypertension.

# ADVERSE EVENTS

Any adverse events as a result of venepuncture will be dealt with in accordance with NHS procedures. The occurrence of any other adverse as a result of participation within this study is not expected and no adverse event data will be collected.

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# TRANSPORT AND STORAGE OF THE TISSUES

Samples will be stored in linked anonymised format within the School of Medicine at Queen’s Medical Centre. Samples will be labelled using a combination of initials and participant number to permit accurate linkage to clinical data.

Blood samples will be stored in aliquots, at either -20 or -80 degrees.

The master database will be held by Dr Mark Glover in a password encrypted file.

The analysis of samples will take place at the University of Nottingham within the Division of Respiratory Medicine. Once analysis has taken place, any remaining samples will be transported back to the Division of Respiratory Medicine at the University of Nottingham and stored within the Research Tissue Bank for future research (DI Prof Jim Lowe- Licence Number 12265) if participants are agreeable and sign the optional clause on the consent form.

Where participants do not agree to the future use of the samples they will be destroyed in accordance with the Human Tissue Act, 2006.

## LABORATORY ANALYSES

Analysis of blood and urinary electrolytes and hormonal profiles will be performed by the biochemistry department at Nottingham University Hospitals NHS Trust using standard techniques employed in routine clinical care.

Western blotting of the 100ml urine sample will be undertaken within the School of Medicine using a standard protocol.

DNA shall be extracted from blood collection samples using standard magnetic bead technology. Technologies to analyse DNA such as targeted resequencing and genome wide association studies are constantly evolving and so detailed description is certain to be outdated by the time of performance.

Genetic data attributable to a single individual will be stored on secure university computer(s) and shall be labelled in a linked- or pseudo-anonymised format. Specifically each individual’s genetic data shall be contained in a file labelled with initials and participant number.

# STATISTICS

### Statistical analysis

Analysis of differences in plasma electrolyte/hormonal profiles, 24 hour urinary electrolyte and urinary sodium transporter profile between cases and controls will be by one way ANOVA with Bonferroni correction.

For future genetic testing standard statistical techniques for genome wide association and variant calling shall be used and analysis shall be subject to peer review during manuscript submission.

### Primary Outcome Measure

The primary outcome measure is a combined primary outcome of mortality, stroke, MI, change in eGFR or need for renal dialysis within 10 years.

# ETHICAL AND REGULATORY ASPECTS

### Ethical Issues

The study will not be initiated before the protocol, informed consent forms and participant information sheets have received approval / favourable opinion from a Research Ethics Committee (REC). Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC. A protocol amendment intended to eliminate an apparent immediate hazard to participants or researchers may be implemented immediately providing that the REC is notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice and Good Laboratory Practice, the UK Department of Health Policy Framework for Health and Social Care, 2017 and in accordance with the Human Tissue Act, 2004.

### Informed Consent and Participant Information

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Study Master File. A second copy will be filed in the participant’s medical notes and a signed and dated note made in the notes that informed consent was obtained for the study.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No study-specific interventions will be done before informed consent has been obtained.

If the Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

### Withdrawal

The investigator will explain that participation in the study is entirely voluntary and that the participant will retain the right to withdraw at any time without prejudice by simply informing the investigator. Should samples and data already have been obtained we will inform the participant that we would still like to use these samples and data and this will be indicated in the information sheet and consent form. Remaining tissue samples will be destroyed if the participant so wishes.

## RECORDS

Each participant will be assigned a trial identity code number, allocated for use on CRFs, other trial documents and the electronic database. The documents and database will also use their initials.

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant’s name, date of birth, local hospital number or NHS number, and Participant Study Number (the Study Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the ‘Study Delegation Log.’

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

### Sample Labelling

Each participant will be assigned a trial identity code number for use on the samples, consent forms and other study documents and the electronic database. The documents and database will also use their initials. Samples for NHS pathology analysis will be labelled in accordance with local NHS procedures.

### Source documents

Source documents shall be filed at the investigator’s site and may include but are not limited to, consent forms, current medical records, laboratory results and records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

### Direct access to source data / documents

Study documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor’s designee and inspection by relevant regulatory authorities.

### Data Protection

All study staff and investigators will endeavour to protect the study participants’ rights to privacy and informed consent, and will adhere to the Data Protection Act, 2018. Only the minimum required information for the purposes of the study shall be collected. Documents will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the study staff and investigators and relevant regulatory authorities (see above). Computer held data including the study database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

Information about the study in the participant’s medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

# QUALITY ASSURANCE & AUDIT

## INSURANCE AND INDEMNITY

Insurance and indemnity for study participants and NHS staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but study participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

## STUDY CONDUCT

Study conduct may be subject to systems audit of the study files for inclusion of essential documents; permissions to conduct the study; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); and equipment calibration logs.

## STUDY DATA

Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Chief Investigator, or where required, a nominated designee, shall carry out monitoring of study data as an ongoing activity.

Data entries will be verified by inspection against the source data. A sample (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on any study databases will be checked. Where corrections are required these will carry a full audit trail and justification.

Study data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

## RECORD RETENTION AND ARCHIVING

In compliance with the DH Research Governance Framework guidelines, the Human Tissue Act and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief Investigator will maintain all records and documents of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The study documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all study databases and associated meta-data encryption codes.

## DISCONTINUATION OF THE STUDY BY THE SPONSOR

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons.

## STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to study data in the computer files.

Data generated as a result of this study will be available for inspection on request by the Sponsor, the REC and representatives of the Human Tissue Authority.

# PUBLICATION POLICY

Results from this study shall be submitted for publication in peer reviewed journals and presentation at national and international meetings. At no stage will personal identifiable information be made public or form any part of data submitted for publication or presentation.

# STUDY FINANCES

### Funding source

Nottingham University Hospitals Charity

### Participant stipends and payments

Participants will not be paid to participate in the study. Unfortunately we are unable to offer travel expenses for hospital visits in excess of usual care.

# REFERENCES

References

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