

CLINICAL STUDY PROTOCOL

**IS Metomidate PET-CT superior to Adrenal venous sampling in
predicting outcome from adrenalectomy in patients with primary
Hyperaldosteronism (MATCH)**

Protocol Version: 2.0
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GRNERAL INFORMATION

2.1 Study Team

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2.2 Protocol Synopsis

Short Title of clinical trial	IS Metomidate PET-CT superior to Adrenal venous sampling in predicting outcome from adrenalectomy in patients with primary Hyperaldosteronism (MATCH)
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Sponsor name	Queen Mary University of London (QMUL)
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Research Identification Number	011149
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Medical condition or disease under investigation	Hypertension/hyperaldosteronism/adenoma
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Purpose of clinical trial	To improve prediction of outcomes from surgical intervention in patients with Primary aldosteronism, and evaluate the merits of non-invasive metomidate PET CT versus adrenal vein sampling in the diagnosis of surgically correctable aldosteronism.
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Primary objective /aim	To assess the aldosterone/renin ratio and blood pressure response of patients with primary hyperaldosteronism recommended for surgery or continued medical management following diagnostic testing with ¹¹ C-metomidate PET-CT and adrenal venous sampling, and to compare the ability of the two diagnostic modalities to distinguish between unilateral and bilateral aldosterone-producing adenoma.
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Secondary objective/aims (s)	<ol style="list-style-type: none">1. To investigate whether measurements during ¹¹C-metomidate PET-CT or AVS improve prediction of outcome after surgery.2. To investigate whether blood pressure response to therapy with spironolactone/eplerenone improve prediction of outcome after surgery
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	<p>3. To investigate whether demographic, genotypic, and pathological data, improve prediction of outcome after surgery</p>
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<p>Study Design</p>	<p>This is an observational cohort study which takes place within existing secondary and tertiary care practice of the NHS. It is a multi-centre study in which all patients have the same two investigations performed in random order. These are as follows:</p> <p><u>11C- metomidate PET CT</u></p> <p>This is a one-hour non-invasive study, prior to which patients are treated with dexamethasone for 3 days.</p> <p><u>Adrenal Vein Sampling</u></p> <p>This is an invasive investigation in which both adrenal veins are cannulated and blood collected for measurement of adrenal steroid hormones. Adrenocorticotrophic hormone (ACTH) is administered prior to AVS in order to ensure steroid hormone secretion during the procedure.</p> <p>We will standardise the start-time of treatment with spironolactone/eplerenone, which is first-choice treatment for patients with primary aldosteronism, in order that the pre-spironolactone blood pressure and biochemistry can be compared with subsequent measurements post-surgery, and the changes during the first month of spironolactone/eplerenone treatment can be used to assess their value in predicting response to surgery.</p> <p><u>Sub-study of Repeat Metomidate PET CT before and after Spironolactone/eplerenone therapy</u></p> <p>In order to determine whether it will be necessary for the start of spironolactone/eplerenone treatment to be delayed in all patients until after both investigations are completed, we will perform a sub-study, early in MATCH, in which 6 patients have their PET CT</p>
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	<p>repeated after at least 6 weeks treatment with spironolactone/eplerenone. (This is the conventional period of time for which spironolactone/eplerenone is withdrawn prior to AVS.)</p> <p><u>Follow-up management and investigations</u></p> <p>We anticipate ~50% of patients will be found on one or both investigations to have unilateral PA, and be recommended for adrenalectomy.</p> <p>The primary outcome measurements will be at 6 months after surgery.</p>
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<p>Study Outcome Measures</p>	<p><u>Primary outcomes:</u></p> <ol style="list-style-type: none"> 1. Change in ARR from baseline to 6 months after treatment 2. Change in SBP (mean of at least 18 measurements from 3 days' home monitoring), from baseline to 6 months after treatment <p><u>Secondary outcomes</u></p> <ol style="list-style-type: none"> 1. Cure of hypertension, defined as the proportion of patients in whom average home blood Pressure measurements 6 months post adrenalectomy are <140/90 mmHg on no treatment. 2. Prediction of cure of hypertension, by one or more of: <ol style="list-style-type: none"> a) The ratio of SUVmax between tumour and normal adrenal; b) Blood pressure fall on spironolactone/eplerenone (50 mg daily for 2 weeks, 100 mg daily for 2 weeks), measured as the difference in home systolic blood pressure c) Post-operative analyses of the APA, to include genotyping for somatic mutations in KCNJ5, CACNA1D, ATP1A1, ATP2B3, CTNNB1 and phenotyping by histological grading (zona fasciculata versus zona glomerulosa), gene expression and immunohistochemistry. 3. Change in home blood pressure from baseline at follow-up visits other than 6 months post-adrenalectomy. 4. Reduction in number of antihypertensive drugs 5. Change from baseline in blood levels of Troponin, Brain Natriuretic Peptide. <p>The judgement as to which patients have met primary and secondary outcomes will be made</p>
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	by a critical endpoints committee meeting every 3-6 months throughout the study.
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Sample Size	The sample size calculation has been performed to permit detection of a significant influence on outcome where the smallest number of patients will be available. This is the group of patients in whom the two diagnostic techniques give discordant results, estimated to be ~20% of the total. Recruitment of 140 patients across 3 centres over 3 years (<1/centre/month), with an estimated 70 proceeding to adrenalectomy, permits 90% power at alpha=0.01 of detecting superiority of PET CT over AVS.
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Study Sites	Approximately 3 sites in the UK
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Summary of eligibility criteria	<p>Inclusion Criteria</p> <ul style="list-style-type: none"> • Male or female: Age >18 yrs. • Diagnosis of PHA based on published Endocrine Society consensus guidelines. • Patients will be enrolled/consented when they have had <u>each</u> of the following: <ol style="list-style-type: none"> 1. At least one paired measurement of plasma renin and aldosterone, measured off spironolactone/eplerenone, showing an elevated ARR. 2. <i>either</i> a plasma aldosterone >190 pmol/L after saline infusion <i>or</i> 'spontaneous hypokalemia + plasma renin below detection levels + plasma aldosterone > 550 pmol/L)' (as per Endocrine Society guidance) 3. a CT or MRI scan of the adrenals with probable or definite adenoma(s) <p>Patients with elevated ARR can be put forward for consideration by the MDT as exceptional cases in whom spironolactone/eplerenone is not (fully) withdrawn, and/or saline suppression is not performed, IF:</p> <ol style="list-style-type: none"> 1. Plasma Aldosterone > 450 pmol/L AND plasma renin <0.5 pmol/ml/hr (<9 mU/L) if measured on treatment with ACEI (Lisinopril >=20 mg or
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	<p>equivalent) or ARB (Losartan 100 mg or equivalent); OR</p> <p>2. Age <40 AND definite adrenal adenoma on CT or MRI</p> <p>Patients whose CT/MRI does not show probable or definite adenoma must also be reviewed by MDT before enrolment/consent</p> <p>All patients will have a positive Aldosterone renin ratio (ARR) serum measurement with another local diagnostic confirmatory test as specified from local specialised APA Guidelines. This is often standard cross-sectional imaging by CT or MR scanning. Any exception to recommended diagnostic criteria will be subject to approval by monthly MDT.</p> <p>Exclusion Criteria</p> <ul style="list-style-type: none"> • Those patients who indicate that they are unlikely to proceed with surgery will not be recruited, because there will be no outcome change in blood pressure, restoration of normal renin/angiotensin physiology) against which to compare the accuracy of the two Investigations. • Patients contraindicated for spironolactone or eplerenone therapy. • Any patients continuing on beta-blockers or direct renin blockers . • Pregnant / breastfeeding females or women unable/unwilling to take secure contraceptive precautions whilst undergoing investigations. • Patients unwilling/unable to take the dexamethasone required to prepare for a metomidate PET-CT scan. • Patients unwilling to have both 11- C Metomidate PET CT scan and Adrenal Vein Sampling. • Any illness, condition or drug regimen that is considered a contraindication by the PI

<p><u>Procedures:</u> Screening & enrolment</p>	<ul style="list-style-type: none"> • Informed consent • Demography • Ethnicity • Body Weight/HT • Medical History, Concomitant medications
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	<ul style="list-style-type: none"> • Clinic BP, using the same provided bp monitor as for home BP readings, in triplicate, after 5 minutes seated rest. • Blood samples will be taken for electrolytes, bicarbonate, renin mass and renin activity, aldosterone and renal function • 12-lead ECG. • Urinalysis 24 hours electrolytes Sodium and Potassium • 24 Urine steroid Profile • HCG for women of child-bearing potential • Inclusion/exclusion criteria checks <ul style="list-style-type: none"> • Enrolment visit subject identification number will be issued and patient notified the order of investigations, Patients allocated to the 11-C-metomidate PET CT scan first will proceed as follows: • Check inclusion and exclusion criteria • Blood pressure monitor provided with training on its use with Pt Blood pressure diary. 3 readings are to be taken morning and evening for 4 days before each clinic visit. • Date provided for scan appt. • Provision of prescription for 0.5mg Dexamethasone with instructions to take 6hrly 3 days before scan. A surplus of tablets to cover for 5 days supply if required. • If patient is on a MR (spironolactone/eplerenone antagonist this will usually need to be stopped 6 weeks before going onto AVS sampling. • Correct potassium depletion following local guidelines.
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Procedures	Screening/Baseline: <ul style="list-style-type: none"> • Informed consent • Medical History/Clinical examination • Demography, ethnicity • Weight, height • Medications • Clinic blood pressure and HR • Blood sampling, urinalysis, urine steroid profile • HCG for women of child-bearing potential • 12-lead ECG • Inclusion/exclusion criteria checks
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	<ul style="list-style-type: none"> • Home blood pressure and HR monitoring provided with training • Pharmacogenetics <p>Prior to 11-C-metomidate PET CT:</p> <ul style="list-style-type: none"> • 0.5mg Dexamethasone to be taken 6hrly 3-5 days before scan <p>Prior to AVS:</p> <ul style="list-style-type: none"> • Spironolactone/eplerenone will usually be stopped 6 weeks before; • Correct potassium depletion, following local guidelines. Bloods for ACTH, cortisol, electrolytes with bicarbonate, urea, creatinine, plasma renin mass and aldosterone <p>Treatment:</p> <ul style="list-style-type: none"> • 11-C metomidate PET CT and AVS results reviewed at specialist MDT <ul style="list-style-type: none"> ○ If lateralisation occurs, patient informed and referred for adrenalectomy ○ Post-operative analyses of aldosterone-producing adenoma (genotyping and somatic mutations) • All patients continue/commence treatment with spironolactone/eplerenone <ul style="list-style-type: none"> • Home blood pressure monitoring prior to each visit • Weight • Medications • Clinic blood pressure • Blood sampling, urinalysis, urine steroid profile • Serious adverse events • HCG testing for CBP females • CMR scan
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Study visits (See also 2.3: Schedule of Assessments and Procedures)	All patients will have five visits for screening and enrolment, for each investigation (PET CT and AVS), and then at the start, middle (2 weeks) and end (4 weeks) of the dose-ranging response to spironolactone/eplerenone. Those continuing on medical treatment alone will have one or two further visits between 9 months and 2 years following MDT decision. Those proceeding to adrenalectomy will have as many as possible of the following visits compatible with the overall study end 4 years after study-start: at 1, 3, 6, 12 and 24 months after adrenalectomy.
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Treatment at study end	It is expected that post adrenalectomy patients will require either no antihypertensive medications or reduced antihypertensive medication which is tailored to their requirements at various points post operatively. For patients who do not proceed to surgery, it is expected that they will continue medical treatment with spironolactone, with change to eplerenone and/or addition of amiloride, if indicated by blood pressure or side effects.
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Procedures for safety monitoring during trial	Serious adverse event reporting, symptom monitoring, BP monitoring and blood tests for creatinine and electrolytes.
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Criteria for withdrawal of patients on safety grounds	New diagnosis which contra-indicates adrenalectomy.
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Adverse events	Selected adverse and all serious adverse events will be recorded onto study database.
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Direct access to source data / documents	The investigators will permit trial related monitoring, audits, REC review, regulatory inspections.
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Ethical considerations	All patients will freely give their informed consent to participate in the study. A patient may decide to
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	<p>withdraw from the study at any time without prejudice to their future care.</p> <p>The study protocol has been submitted (</p>
Indemnity	<p>Negligence in protocol writing will be covered by QMUL (Queen Mary University of London insurers. Negligence in execution of the protocol will be covered by QMUL insurers.</p> <p>There will be no non-negligence cover.</p>
Emergency contacts	<p>Local PI at each site, as above.</p>

2.3 Schedule of Assessments and Procedures

<u>Time Point</u>	<u>Screening & Enrolment</u>	<u>C-11 Metomidate PETCT scan</u>	<u>AVS Sampling</u>	<u>Baseline</u>	<u>2week Post spiro 50mg</u>	<u>2week Post spiro 100mg</u>	<u>MDT** Meeting Pts for surgery only continue to 4 weeks' post- surgery</u>	<u>4weeks post- surgery</u>	<u>3 months post-surgery</u>	<u>6months post surgery</u>	<u>9 months</u>	<u>1 year post surgery</u>	<u>2 year post surgery</u>
Informed consent	X												
Medical history	X												
Clinical examination	X												
Concomitant medications	X												
weight	X												
Ethnicity	X												
Inclusion/Exclusion	X												
Clinic BP/HR	X			X	X	X		X	X	X		X	X
Home BP and HR				X	X	X		X	X	X		X	X
12 lead ECG	X			X						X			
Dexamethasone Prep 6hrly 3 days prior to PET CT		X											
avs samples. aldosterone cortisol													
Blood tests – electrolytes with bicarbonate, urea, creatinine, before scan	X	X		X	X	X		X	X	X		X	X

ACTH (before scan)		X	X										
High-sensitivity Troponin				X					X	X			X
BNP				X					X	X			X
Blood tests – plasma renin mass , renin activity and Aldosterone	X	X		X				X	X	X		X	X
Serum Cortisol		X											
Pharmacogenetics ¹	X												
24 hour urinary electrolytes sodium/potassium				X									
Urinalysis	X												X
24hr Urine Steroid Profile				x									
HCG testing for CBP	X	X	X	X	X	X		X	X	X		X	X
2mls sample plasma collected from spun EDTA and frozen				X									
Serum sample collected spun and frozen				X									
CMR surgical***				X						X			
CMR non-surgical***											X		

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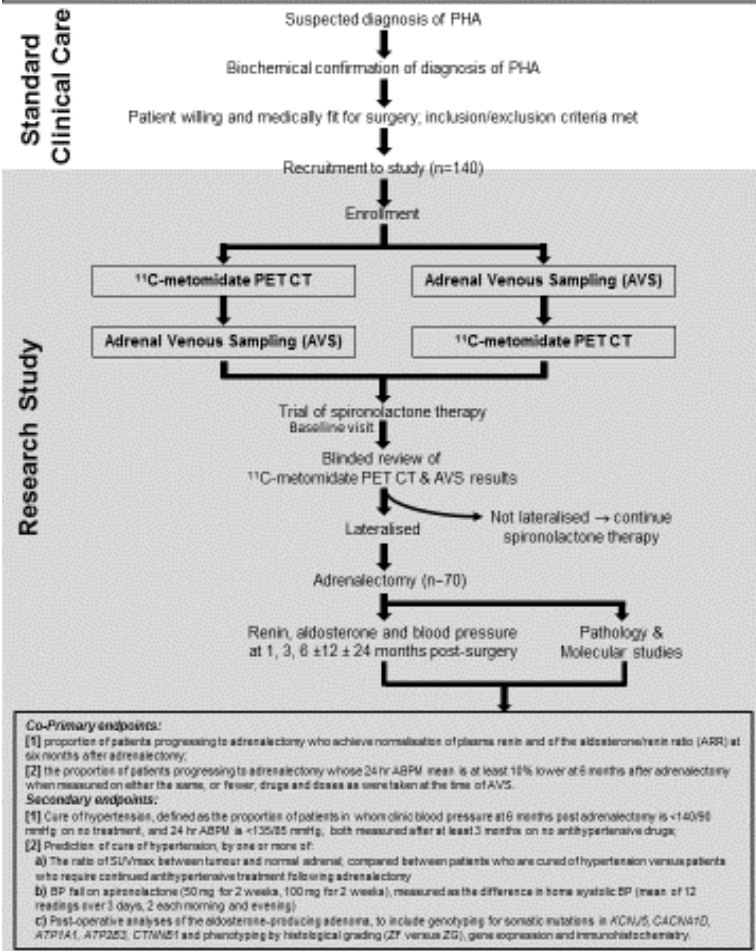
***For patients not having surgery next study visit will be 9-12 months and another up to 2 years following MDT review of PET CT/or and Adrenal Vein Sampling**

****** There will be monthly MDTs, with the aim of having a decision for most patients that is discussed with them at their visit after 4 weeks of spironolactone/eplerenone.

******* CMR can be done any time before spironolactone/eplerenone treatment and following 6 weeks withdrawal from amiloride, eplerenone and/or spironolactone.

Follow up 6 month CMR scan can be done after 6 month time point but before the 12 month time point.

Is Metomidate PET CT superior to Adrenal venous sampling in predicting outcome from adrenalectomy in patients with primary Hyperaldosteronism (MATCH): a randomised within-patient comparison of diagnostic techniques



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Flow Chart for MATCH study

Medical Background

Hypertension is a major risk factor for heart attacks and stroke. Primary hyperaldosteronism (PHA) is an important cause of hypertension and is characterized by excessive aldosterone production by one or both adrenal glands. Previously thought to account for less than 1% of cases of hypertension, there is now general consensus that this is an underestimate, with various series reporting a prevalence of 6-15% in unselected hypertensive populations and up to 20-25% of individuals whose blood pressure is resistant to therapy.(1-5) Uncontrolled hypertension *per se* is thought to cause 350 preventable strokes and major cardiac events per day in the UK but, in addition, PHA itself carries significant cardiometabolic risk over and above that conferred by elevated blood pressure alone.(6) Stroke, myocardial infarction and atrial fibrillation are increased 4 to 12 fold compared to age, gender and blood pressure-matched subjects with essential hypertension. Recent surveys suggest that ~12 million people in the UK have hypertension and over 1 million are therefore likely to have PHA-mediated hypertension.(7) This figure is in line with the recently reported estimate for the USA of at least 10 million affected Americans.(8)

Although various rare forms of PHA exist, the vast majority of cases are accounted for by either bilateral adrenal hyperplasia (BAH) or (in approximately 50% of cases) a unilateral aldosterone-producing adenoma (APA). Distinguishing unilateral from bilateral disease is important, as the ideal (potentially curative) treatment for an APA is surgical removal by laparoscopic adrenalectomy (a low-morbidity procedure in experienced surgical hands), whereas BAH is most appropriately managed medically with aldosterone antagonists.(9-11) Using even the most conservative of the above prevalence estimates, at least 360 000 people in the UK (and probably closer to 500 000) will have a unilateral APA as the cause of their hypertension, making it easily the most common cause of surgically curable hypertension.

Current deficiencies in clinical care

In recent years detection rates of PHA in both primary and secondary care have improved significantly, largely consequent upon the greater availability of high throughput renin assays.(3,12,13) However, in current UK clinical practice, only a tiny proportion of patients with PHA complete the investigational pathway and are referred for potentially curative surgery.

One of the main barriers is the difficulty of proving that only one adrenal gland is the culprit. On diagnostic cross-sectional imaging (CT or MRI), smaller (<1 cm) adenomas may be overlooked (particularly if they lie within the body of the adrenal gland) while, conversely, incidental non-secreting adrenal adenomas occur in 4% of the population over the age of 40 years.(14,15) The latter issue means that in a significant minority of patients with PHA a focal adrenal lesion seen on imaging will not be the source of aldosterone excess and its surgical removal would be inappropriate.

Currently, the test widely considered to be most accurate in distinguishing unilateral (surgically-treated) from bilateral (managed medically) disease is adrenal venous sampling (AVS). This diagnostic procedure, involving the successful cannulation of both 1mm diameter adrenal veins is difficult, time-consuming, invasive, available in only a few centres and has variable success rates, depending on technical expertise and the diagnostic criteria employed.(16,17) Inevitably, therefore, many PHA patients with surgically-remediable hypertension are suboptimally treated.

Hospital Episodes Statistics indicate that fewer than 300 adrenalectomies for PHA are performed in the UK – far behind, *pro rata*, other Western European countries (Reincke M and Plouin F, personal communication from the German Conn's registry and the European Study of Adrenal Tumours). Given the above prevalence figures, this represents a major shortfall in clinical care, with public health consequences that are hard to overestimate. A second reason that physicians are seemingly reluctant to complete the assessment of PHA by looking for a resectable APA is that the chances of 'cure' of hypertension following adrenalectomy are difficult to predict, making surgical recommendations for individual patients problematic, especially in older patients.(10,11) The purpose of this proposal is to conduct a multi-centre clinical study to provide data that will address both these issues and, thereby, improve the major shortcomings in clinical care currently offered to patients with PHA.

¹¹C-metomidate scanning

Metomidate is a potent inhibitor of CYP11B1 (11 β -hydroxylase) and CYP11B2 (aldosterone synthase). It is the methyl analogue of etomidate, an ethyl-imidazole anaesthetic agent which is used clinically in sub-hypnotic doses as an inhibitor of adrenal steroidogenesis in the management of refractory Cushing's syndrome.(18,19) Metomidate (itself used as a veterinary anaesthetic until the 1970's) can be C¹¹H₃-labelled as a PET radiotracer (¹¹C-metomidate), and proof of concept of its high affinity binding to adrenal cortex was established *in vitro* and in primate studies as far back as 1998.(20) In the first human application, 15 patients underwent ¹¹C-methionine imaging prior to surgery for a unilateral adrenal mass.(21) The nine histologically-diagnosed adrenocortical tumours each demonstrated high uptake and could be reliably discriminated from the six lesions which were not of cortical origin. In a larger follow up series, comprising 73 patients who underwent surgery for suspected adrenal lesions, the six histologically confirmed APAs demonstrated the highest ¹¹C-metomidate uptake, with a standardised uptake value (SUV) of 30.7 compared to 18.4 in non-functional adenomas.(22) When combined with high-resolution CT scanning its sensitivity and precision both increase as the improved spatial resolution permits distinction of tumour from normal adrenal tissue (and separate measurement of SUV in each) with greater confidence.(23)

In a previous, non-randomised proof-of-concept study we showed that ¹¹C-metomidate PET CT scanning is comparable to AVS in distinguishing unilateral from bilateral PHA.(24) In 35 patients with confirmed PHA and an anatomical adrenal abnormality, ROC analysis for PET-CT showed that the finding of >25% higher PET signal (SUVmax - maximum standardised uptake value) over an adenoma compared to the contralateral adrenal conferred 76% sensitivity and 87% specificity compared to AVS; specificity rose to 100% in patients whose absolute SUVmax over tumour was >17. Since then, considerable clinical experience with ¹¹C-metomidate PET-CT scanning has been accumulated, although robust, randomized trial data are lacking to endorse its widespread use as the investigation of choice.(23,25)

3.1 Hypothesis and Novel Aspects of the Trial

Our hypothesis that ¹¹C-metomidate scanning is superior to AVS derives from the findings of our earlier study, and subsequent clinical experience in more than a hundred patients. We now wish to determine whether ¹¹C-metomidate scanning is superior to AVS in identifying unilateral PHA. Despite our experience, most individual centres, and importantly the forthcoming revision to the American Society of Endocrinology Guideline, are waiting for further trial data, albeit acknowledging that PET CT is likely to have a major role in sub-typing of PHA. If superiority of

PET-CT can be shown then this, coupled with greater patient preference and convenience, would improve access to diagnosis and will encourage doctors to look for PHA in many more patients than is currently the case. Another major challenge in the management of unilateral PHA is the successful preoperative identification of those patients who are likely to benefit most from adrenalectomy. It is timely therefore to investigate whether ^{11}C -metomidate PET-CT and clinical response to spironolactone, together with demographic, genotypic and pathological data, can provide predictive information as to which patients should be prioritised for surgery. The case that ^{11}C -metomidate PET-CT will be superior to AVS

Aside from the obvious advantages of being non-invasive and, potentially, affording greater capacity for investigating PHA (only a handful of interventional radiologists in the UK are able to perform AVS to a good standard), there are several reasons why we consider ^{11}C -metomidate PET-CT is likely to be superior in distinguishing unilateral from bilateral disease. First, international consensus criteria on the interpretation of AVS demand stringent thresholds to reliably establish whether excessive aldosterone production lateralises to one side or the other.(17) Aldosterone (A) and cortisol (C) values are measured in both adrenal veins and in the lower part of the inferior vena cava (IVC), and a 'normalised' aldosterone value (A/C ratio) calculated for each side. Evidence of lateralisation (i.e. 'dominance' of aldosterone production by one adrenal gland) is considered to be present if (i) the A/C ratio on one side is ≥ 4 times that on the other side **and** (ii) the A/C ratio in the 'non-dominant' (or 'suppressed') vein is less than that in the IVC. BAH is diagnosed if the A/C values in each adrenal vein differ by ≤ 2 -fold, which leaves an equivocal ('grey') area (A/C ratio of 2-4) in which clinical decision-making is controversial.(26)

As already indicated, given that many physicians are inherently reluctant to pursue PHA investigations to their conclusion, clinical caution dictates that a substantial proportion of patients with ambiguous or non-diagnostic results from initial AVS do not progress to further investigation or surgery. Second, it is an important requirement for AVS that patients discontinue spironolactone (or other mineralocorticoid receptor antagonists) several weeks before the procedure in order to avoid a false negative result due to re-activation of aldosterone secretion from the contralateral (normal) adrenal. However, patients with difficult-to-control hypertension and/or hypokalaemia are exposed to potential risk by this practice. It is also important to avoid hypokalaemia at the time of AVS, which itself can blunt aldosterone secretion from the APA and thus contribute to a false negative catheter study. For patients who develop marked hypokalaemia on discontinuing potassium-sparing diuretic therapy, the requirement to take large amounts of potassium supplements to achieve normokalaemia is unpalatable and, in many cases, unsuccessful. In contrast, ^{11}C -metomidate scanning does not require the discontinuation of spironolactone. Third, it is being increasingly recognised that in a significant proportion of patients, what may have appeared to be a single focal lesion within one adrenal gland is, on histological examination, a series of discrete, smaller nodules.(27,28) The anatomical/functional 'model' on which interpretation of AVS is based, is one of a homogeneously draining adrenal effluent, but our *ex vivo* experiments on adrenals removed at surgery clearly indicate these smaller nodules may have different secretory activity. For example, an APA may exist alongside a nodule with high expression of CYP11B1 (encoding the enzyme that produces cortisol). Given the stringent criteria described above, any change in the denominator of A/C has the potential to alter the interpretation of the AVS result and change surgical decision making. Our experience indicates that ^{11}C -metomidate scanning is not subject to this potential confounding factor.(23-25)

Increasingly, we are also using ^{11}C -metomidate PET CT to identify small APAs which were missed altogether on original cross-sectional imaging by CT or MRI (Appendix A Case 4). These

small APAs often prove to be zona glomerulosa (ZG)-like on appearance and laboratory analyses, and we believe the high density of metomidate uptake reflects their high density of aldosterone synthase.

Finally, the PET CT also appears valuable in excluding unilateral disease in patients where AVS has been ambiguous or unsuccessful

Pre-treatment with spironolactone as a predictor of outcome following surgery

Aside from the lack of widespread availability of high quality AVS, surgical decision-making in PHA is made more difficult by the lack of a good ‘prediction’ test to indicate who will benefit most from a unilateral adrenalectomy.(11) In younger patients (particularly females planning to conceive), with a shorter duration of hypertension, the avoidance or reduction in number of long-term antihypertensive agents almost always outweighs the temporary discomfort of surgery. However, in older patients the decision may be more balanced, particularly in the presence of comorbidities and if the number of agents required to control blood pressure is modest. We hypothesize that a preoperative therapeutic trial of spironolactone (an aldosterone antagonist), using a strictly defined protocol, will provide information to aid prediction of which patients are likely to derive the greatest benefits in terms of blood pressure control following surgery. Using higher doses, but for a relatively short time period (4 weeks), should permit more complete mineralocorticoid receptor blockade than is often achieved in routine clinical practice, while avoiding the side effects (e.g. gynaecomastia in men; menstrual disturbance in premenopausal women) that are typically associated with long-term use.

¹¹C-metomidate scanning as a tool for predicting outcome following surgery. In addition to the above, it is timely and plausible to explore whether ¹¹C-metomidate PET CT can recognise differing types of APA with intrinsic differences in prognosis. We see these efficacy and mechanism evaluations as the vital middle step in progressing the technique from its BHF-funded experimental proof-of-concept to HTA-assessment as the nationally (and internationally) preferred technique for optimal and cost-effective decision making in PHA.

Rationale for undertaking tumour genotyping to enable prediction of outcome

Currently, approximately two thirds of unselected APAs harbour somatic mutations in one of several recently identified genes (*KCNJ5*, *ATP1A1*, *ATP2B3*, *CACNA1D*, *CTNNB1*) (27,29) It remains unclear whether APAs harbouring particular mutations may have inherent differences in their natural history and the clinical outcome following their surgical removal. Our group is developing techniques and protocols (not included in this grant proposal) to identify the presence of mutations in DNA derived from adrenal effluent blood (obtained during AVS – as a proof-of-concept step in the pathway to screening blood from a peripherally collected sample(30)), and from fine needle aspirates obtained by endoscopic ultrasound. Developing a prediction model that includes the retrospective genotype information obtained from the tumours of patients included in this study opens up the potential, in the future, for stratified clinical decision-making using genotypic information obtained by the two novel approaches described.

The potential for ‘digital’ quality diagnosis, by detection of somatic mutations seen uniquely in unilateral APAs, will be increased if the proportion of APAs with known mutations rises from the current 60-70%, towards 80-90%. A greater variety of mutations would also increase the possibilities for linking outcome to genotype. We therefore plan two complementary pieces of genotyping on each APA. One is targeted sequencing of all known genes with adrenal mutations, using an Ion Torrent Custom Panel, commissioned by Prof Eamonn Maher (Genetics). The

remaining samples will be submitted to exome sequencing at the end of the project, by when cost is expected to be as low as the targeted sequencing now costs.

3.2 Risk-Benefit Considerations

Risks: We consider the potential risks to patients who participate in MATCH to be very small. The radiation dose of an ^{11}C -metomidate PET-CT scan has been estimated at 3.5 mSv - slightly higher than a year's exposure to background radiation (2.7 mSv - <https://www.gov.uk/government/publications/ionising-radiation-dose-comparisons/ionising-radiation-dose-comparisons>), and substantially lower than that associated with a chest CT scan (6.6 mSv) and the minimum level, 10 mSv, to raise any concerns about imaging studies. For the sub study of 6 patients, the dose for the two PET CT scans before and after spironolactone therapy, this exposure is approximately 10.75 millisieverts (mSv) equivalent to 4 years' exposure to background radiation in the UK. This equates to approximately estimated at about 1 in 2100 risk of developing cancer and to put this into context, the natural life time incidence of developing cancer is estimated to be about 1 in 3.

As described, the group of patients to be studied are those with PHA who indicate a desire to proceed with laparoscopic surgery if the diagnostic tests support a unilateral source of aldosterone excess. The discomfort from surgery is something that would occur with routine clinical management and is not considered to be 'study related'. If our hypothesis is correct, that ^{11}C -metomidate scanning is superior to AVS, then clearly more patients will experience the discomfort of surgery. However, given that the stated goal of the project is to increase the numbers of patients offered potentially curative surgery prior to the onset of irreversible hypertension we consider this outcome to be a potential benefit rather than a risk.

Benefits: The potential benefit to patients is that, if the hypothesis is correct, more patients will proceed to adrenalectomy than do so based on conventional testing; moreover, at least 50% of these will be cured of their hypertension altogether, and the remainder will require fewer drugs for effective blood pressure control. Therefore, aside from the potential benefits to individuals, society also stands to gain from MATCH with a reduction in the public health burden from poorly controlled hypertension and its sequelae in a large number of patients.

4.0 OBJECTIVES

4.1 Assessment of Efficacy and Safety

Efficacy will be determined by changes in ARR and BP following treatment, guided by ^{11}C -metomidate PET-CT and AVS.

Safety will be assessed by monitoring symptoms, BP, renal function and serious adverse events at each visit.

4.2 Primary Objectives/Aims

To assess the aldosterone/renin ratio and blood pressure response of patients with primary hyperaldosteronism recommended for surgery or continued medical management following diagnostic testing with ^{11}C - metomidate PET-CT and adrenal venous sampling, and to compare the ability of the two diagnostic modalities to distinguish between unilateral and bilateral aldosterone-producing adenoma.

4.3 Secondary Objectives/Aims

1. To investigate whether measurements during ^{11}C -metomidate PET-CT or AVS improve prediction of outcome after surgery.
2. To investigate whether blood pressure response to therapy with spironolactone/eplerenone improve prediction of outcome after surgery
3. To investigate whether demographic, genotypic, and pathological data, improve prediction of outcome after surgery

5.0 TRIAL DESIGN

The study takes place within existing secondary and tertiary care practice of the NHS and is a multi-centre, prospective, within-patient comparison of the diagnostic accuracy of AVS and ^{11}C -metomidate PET-CT, performed in random order.

Proof of concept in humans has already been demonstrated for ^{11}C -metomidate PET-CT in a published non-inferiority study of 35 patients.(24) This proposal seeks to establish if PET-CT is superior to AVS in its ability to identify surgical candidates.

This is an observational cohort study which takes place within existing secondary and tertiary care practice of the NHS. It is a multi-centre, study in which all patients have the same two investigations performed in random order.

These are as follows:

^{11}C - metomidate PET CT

The specialised abdominal PET CT scan locates the hot spots of aldosterone synthase activity of the affected adrenal gland. The Standard ^{11}C - metomidate PET CT scan procedure will be managed in specialised sites where a cyclotron is available to synthesise the radionuclide ^{11}C - metomidate .Currently the diagnostic ^{11}C - metomidate PET CT scan is managed at the PET CT unit Addenbrookes Hospital, Cambridge University Hospitals Cambridge. However other units are including this technique predominantly in London and hope to join within the next two years. Patients will be recompensed for reasonable travel expenses incurred.

Prior to 11-C metomidate scan PET CT scan patients will be prescribed Dexamethasone for three up to five days prior to the scan; one tablet four times a day (one tablet every 6 hours), with the last dose being taken on the morning of the scan or at midday if the scan appointment is in the afternoon. Dexamethasone suppresses the release of cortisol from the adrenal gland allowing aldosterone levels to be measured more accurately by dampening the background noise.

On the day of the scan the patient will be cannulated Baseline bloods will be measured for ACTH, cortisol, electrolytes including urea and creatinine, renin mass, aldosterone and bicarbonate. Following this an Intravenous preparation of 11C-Metomidate radiotracer, after 30 minutes the patients will have the PET CT scan in the specialist unit. 11C-Metomidate has a very short radioactive half-life (20 minutes). This means that there is effectively none of the radiotracer left in the body two hours after the injection.

Dexamethasone: is used diagnostically in clinical practice to assess adrenal gland function. It is commonly used to treat a variety of conditions including allergy. Side-effects usually occur in people who take the medicine long-term with possible side effects including reduced bone density and a compromised immune system. Short term Side-effects are almost always reversible and will go away after treatment is complete. These include indigestion, excess in hunger, changes in glucose levels, changes in mood and difficulty in sleeping. The 11-C metomidate PET CT has been conducted in more than 200 patients, and there have been no reported side effects in these patients from either the dexamethasone or metomidate.

Adrenal Vein Sampling (AVS)

This test is currently the gold standard diagnostic technique for diagnosing Conn's adenoma. The test is carried out in the radiology department by a specialist radiologist. During the first two hours the patient will be cannulated and ACTH (Adrenocorticotrophic hormone) infused in 0.9% saline for 3 hours approximately, commencing half an hour before and continued during the procedure. This is routinely used in the AVS procedure to stimulate the adrenal glands. This maximises the chances of detecting a difference between the two glands and aldosterone production. This is a common clinical diagnostic test in clinical practice.

A small cannulae and catheter are introduced via the groin (usually into the right) to access the blood vessels by the radiologist. Through the needle the catheter is introduced and then positioned in adrenal gland veins. The blood samples from both adrenal veins, and the main vein (inferior vena cava) are used to measure the levels of adrenal hormones, aldosterone and cortisol. These are routine measurements in the AVS procedure the current gold standard. Blood which is not used for these assays will be kept frozen for the development of future tests which may improve our ability to predict outcome from adrenalectomy. These are likely to be additional steroids, secreted proteins, or cell-free RNA or DNA.

Post procedure, patients are to lay flat. During this time, the right groin is routinely inspected to make sure there is no oozing from the site or any significant bruising. Blood pressure and heart

rates are monitored. Patient will be discharged by radiologist. The risk of the procedure we are looking to minimise here is excessive bleeding or haemorrhage afterward. This is rare. There is a potential, although very rare of an adrenal infarction.

Cardiac Magnetic Resonance Imaging scan (CMR)

All patients will be requested to have a cardiovascular magnetic resonance scan (CMR) at baseline visit which will be repeated at the 6-12 months' time point, following baseline visit. CMR uses a powerful magnet and radio waves to form pictures of the heart. Gadolinium-based intravenous MR contrast will be administered via an intravenous cannula for angiography, myocardial perfusion and viability. The incidence of developing adverse events following administration is very low. Most reactions are mild and include warmth, coldness and pain at cannula site, headache, vomiting, parathesias, dizziness and itching. Very rarely, between 0.001% to 0.01% an anaphylactoid reaction may occur. The CMR suite, at St Bartholomew's NHS Trust, have trained clinical staff to manage this condition if it should occur. Patients will have renal function blood tests prior to scan. Patients will be requested to arrive approximately 30 minutes before the actual scan appointment time to perform a brief assessment and change into a gown. The scan itself takes about forty minutes. It involves patient lying in supine position inside a large open-ended tube. Electrocardiogram monitoring will continue during the scan. Patients will be asked to hold breath between 2 and 15 seconds prior to image capture. Patients will be able to communicate the operator anytime via telecon.

Sub-study of Repeat Metomidate PET CT before and after Spironolactone/eplerenone therapy

In order to determine whether it will be necessary for the start of spironolactone/eplerenone treatment to be delayed in all patients until after both investigations are completed, we will perform a sub-study, early in MATCH, in which 6 patients have their PET CT repeated at least after 6 weeks treatment with spironolactone/eplerenone. (This is the conventional period of time for which spironolactone is withdrawn prior to AVS.)

5.1 Follow-up management and investigations

We anticipate ~50% of patients will be found on one or both investigations to have unilateral PA, and be recommended for adrenalectomy.

The primary outcome measurements will be at 6 months after surgery.

5.2 Stopping Criteria

Withdrawal criteria for individual patients are shown in section 4.1 page 26 below. Criteria for the whole trial will be determined by the Trial Steering Committee (TSC), or delegated (if deemed appropriate by the TSC) to an independent DMEC (see [12]). Because neither technique is new, it is highly unlikely that any stringent safety boundary that is set will be crossed. Any stopping rules will need to acknowledge that there is a long lag between the interventions and the assessment of outcome: at least 9 months, given the 6-month post-operative timing of primary assessment, the interval between diagnostic intervention and surgery, and frequency of the endpoint committee assessments.

5.3 Study population

The potential constituency of patients at which MATCH is directed is the majority of all patients with PHA who indicate a desire to proceed to surgery if lateralisation can be confidently shown. The diagnostic criteria for PHA used in all participating centres will be drawn from the recently published updated Endocrine Society consensus guidelines (2016).(31) All patients will have had standard cross-sectional imaging by CT or MR scanning.

5.4 Inclusion/Exclusion criteria:

Inclusion Criteria

- Male or female: Age >18 yrs.
- Diagnosis of PHA based on published Endocrine Society consensus guidelines.

Patients will be consented and subsequently

2. at least one paired measurement of plasma renin and aldosterone, measured off spironolactone eplerenone, showing an elevated ARR. Each hospital should follow their own, or referring hospital's, threshold for ARR. If this is not known or defined, the default is >750 when aldosterone is measured as pmol/L, and renin is measured as renin activity, in pmol/ml/hr.
2. *either* a plasma aldosterone >190 pmol/L after saline infusion
or 'spontaneous hypokalemia + plasma renin below detection levels + plasma aldosterone > 550 pmol/L)' (as per Endocrine Society guidance)
3. a CT or MRI scan of the adrenals with probable or definite adenoma(s)

Patients with elevated ARR can be put forward for consideration by the MDT as exceptional cases in whom spironolactone/eplerenone is not (fully) withdrawn, and/or saline suppression is not performed, IF:

3. Plasma Aldosterone > 450 pmol/L **AND** plasma renin <0.5 pmol/ml/hr (<9 mU/L) if measured on treatment with ACEI (Lisinopril ≥20 mg or equivalent) or ARB (Losartan 100 mg or equivalent); OR
4. Age <40 **AND** definite adrenal adenoma on CT or MRI

Patients whose CT/MRI does not show probable or definite adenoma must also be reviewed by MDT before enrolment/consent

- All patients will have a positive Aldosterone renin ratio (ARR) serum measurement with another local diagnostic confirmatory test as specified from local specialised APA Guidelines. This is often standard cross-sectional imaging by CT or MR scanning. Any exception to recommended diagnostic criteria will be subject to approval by monthly MDT.

Exclusion Criteria

- Those patients who indicate that they are unlikely to proceed with surgery will not be recruited, because there will be no outcome change in blood pressure, restoration of normal renin/angiotensin physiology) against which to compare the accuracy of the two Investigations. Patients contraindicated for spironolactone/eplerenone therapy use.
- Any patients continuing on beta-blockers or direct renin blockers.
- Pregnant patients or women unable/unwilling to take secure contraceptive precautions whilst undergoing investigation.
- Patients unwilling/unable to take the dexamethasone required to prepare for a metomidate PET-CT scan
- Patients unwilling to have both 11- C Metomidate PET CT scan and Adrenal Vein Sampling.
- Any illness, condition or drug regimen that is considered a contraindication by the PI

NB: Patients unable to have baseline cardiac MRI due to claustrophobia per se may still be to included in the MATCH study at the PI discretion.

All other patients with PHA however, are potential candidates for inclusion in MATCH, including those with apparently normal bilateral adrenal morphology, given that small APAs lying within the body of the adrenal may not be seen on even high resolution CT scanning.

Withdrawal criteria:

Unwillingness or inability to undergo both PET CT and AVS or at the PI discretion.

6.0 PLANNED INTERVENTIONS

The primary control intervention is AVS and will be performed according to an identical protocol at all centres whose internal audit data indicate a successful bilateral cannulation rate of >75%. Briefly, the femoral vein is cannulated under local anaesthesia and catheters advanced under fluoroscopic guidance into each adrenal vein.(17) The procedure is performed under conditions of ACTH stimulation, which facilitates unequivocal confirmation of secure adrenal vein cannulation. Blood samples from both adrenal veins and the lower part of the inferior vena cava are analysed for aldosterone (A) and cortisol (C) and an aldosterone/cortisol (A/C) ratio calculated at each site. Lateralisation (providing evidence for an adrenalectomy to be recommended) is deemed to exist if the A/C value in one adrenal vein is at least 4-fold higher than the other. In preparation for AVS, treatment to control blood pressure is limited to a non-dihydropyridine calcium antagonist (e.g. verapamil) and doxazosin (together with potassium supplementation as needed), as the treatments least likely to interfere with interpretation of aldosterone/renin measurements. Although some rise in blood pressure is permitted in preparation for AVS, severely hypertensive patients may require additional therapy according to clinical judgement.

The experimental intervention is ¹¹C-metomidate PET-CT. There has been no change in the protocol used since the proof-of-concept study. Patients are treated with dexamethasone 0.5 mg 6-hourly for 3 days, then receive an injection of 250 mBq (on average) of ¹¹C-metomidate, with CT and PET scanning of the adrenal area 20-30 minutes later. A positive (lateralization) result is indicated by a maximum standardised uptake at least 25% greater in one adrenal gland compared to the other.

The assessment of the two diagnostic modalities will be undertaken at a monthly MDT of endocrinologists and radiologists. Patients will be offered surgery if one or both techniques indicate unilateral disease. For the very small number of cases (we estimate 1 in 25 on the basis of the proof-of-concept study), where AVS and ^{11}C -metomidate PET-CT each meet these criteria for lateralisation, but to opposite sides, we will defer to the Trial Steering Committee (TSC) (see section 11).

The primary outcome is cure of PHA by unilateral adrenalectomy and will be determined by an endpoint committee blind to results of the prior imaging tests.

The secondary intervention is a systematic evaluation of spironolactone/eplerenone therapy, as a predictor of primary or secondary outcomes. After both diagnostic investigations (AVS and ^{11}C -metomidate PET-CT) have been performed, spironolactone/eplerenone will be prescribed in a standardised fashion with home blood pressure monitoring before and after four weeks of treatment (50 mg/day for two weeks, force-titrated to 100 mg/day after two weeks unless SBP is <130 mmHg on repeat home monitoring, and/or plasma K⁺ is >5.0).

In addition to the clinical interventions, we plan a number of laboratory procedures to confirm that the adenoma(s) removed at surgery were aldosterone-secreting, and to look for genetic and/or biochemical differences between APAs. These differences, if observed, will then be correlated with either prior differences in the ^{11}C -metomidate PET-CT signal and/or the subsequent outcome from surgery. The techniques for these laboratory procedures (immunohistochemistry for CYP11B1 and CYP11B2, qPCR for *CYP11B1*, *CYP11B2*, *CYP17A1*, and primary cell culture for measurement of aldosterone secretion) are all well-established in our laboratory. Targeted sequencing of genes with known somatic mutations will also be performed, as described above.

7.0 REQUIREMENTS FOR PARTICIPATING INVESTIGATORS AND TRIAL SITES

All participating investigators must agree to conduct the trial in accordance with the European Clinical Trials Directive 2001/20/EC, local law, the declaration of Helsinki including all revisions, and the study protocol.

Participating sites must have the facilities and resources required for the conduct of the various defined study tests and procedures. For the specialised ^{11}C -metomidate scan patients will be referred to Addenbrookes Hospital Cambridge PET CT Unit.

Training materials will be provided for use of the eCRF system, plus any study-specific procedures as required.

7.1 Trial Sites and Number of Trial Subjects

A total of 140 patients will be recruited into the study, from approx. 6 study sites within the UK.

7.2 Expected Duration of Trial

In total, each participant will be in the study for 2.5 years (including follow up period of 24 months). It is estimated that the total duration of the trial will be 4 years.

8.0 PREMATURE TERMINATION

8.1 Premature Closure of a Trial Site

If protocol compliance is found to be poor at a particular site, or if the data quality is found to be unacceptable, efforts will be made to eradicate the problem (e.g. by additional training). However, if problems persist in spite of these efforts, premature closure of the site will be considered.

Premature closure of a site will also be considered if recruitment is particularly poor at that site.

Future follow-up and treatment of study participants from that site will be agreed by the Steering Committee.

8.2 Premature Termination of the Trial

Premature termination of the trial will be considered in the event of

- new insight from other trials
- insufficient recruitment rates

The decision to terminate the trial will be taken by the Trial Steering Committee.

9.0 SELECTION OF TRIAL SUBJECTS

Patients will be identified from endocrine hypertension clinics

NB: All other patients with PHA however, are potential candidates for inclusion in MATCH, including those with apparently normal bilateral adrenal morphology, given that small APAs lying within the body of the adrenal may not be seen on even high resolution CT scanning.

9.1 SCREENING OF ELIGIBLE PATIENTS

Examination of the inclusion and exclusion criteria of potentially eligible patients will be performed using a predefined screening log. All screened patients, whether eligible or not, should be included in the screening log, with reason for ineligibility recorded as appropriate.

9.2 INFORMED CONSENT

Written informed consent is required before any study-related procedures are carried out.

The patient will be sent the Patient Information Sheet in advance of their visit. The investigator/Research nurse will explain to the potential participant the purpose of the trial, any potential risks involved, the nature of the intervention, and the duration of trial participation. The patient will be informed that participation in the trial is voluntary, and that they may withdraw at any time without compromising either their future care or their relationship with their responsible physician.

The patient will be given time to consider their decision, and to discuss with the study doctor and nurse any questions about the study. If the patient is willing to participate in the trial, the study nurse will obtain the patient's informed consent: the patient will sign a consent form for study participation. The original signed consent form will be retained in the study site file, with copies added to the patient's medical notes and provided to the patient, together with the patient information sheet.

Patients unable to have cardiac MRI due to claustrophobia per se can still consent to MATCH study minus the Cardiac MRI.

9.3 WITHDRAWAL OF INFORMED CONSENT

In the event that a patient wishes to withdraw consent for participation in the trial, this information will be recorded on the study conclusion page, of the eCRF noting the date of withdrawal of consent, together with the reason for withdrawal (if the patient provides that information). The patient will be reassured that their future care will not be affected by their withdrawal, and that their relationship with their responsible physician remains unaltered. The patient will be informed that any of their study data already stored will be retained, and will be used, if necessary, in the evaluation of the study drugs and for adherence to the relevant regulatory requirements.

Patients may withdraw consent for the pharmacogenetic research without affecting their participation in the study as a whole. A pharmacogenetic consent withdrawal form will be completed and signed by the patient. It will record confirmation that the sample has been destroyed.

10.0 ENROLMENT

Before enrolment onto the study, the investigator will confirm that the patient meets all of the study inclusion criteria and none of the study exclusion criteria. Enrolment and allocation of patient ID will be carried out electronically via the eCRF and this system will prevent patients from being enrolling if they do not meet these inclusion/exclusion criteria requirements. This Patient ID will allow clinician to provide patient with order of procedures. The Patient ID acts as an identifier for return visits.

10.1 VIOLATION OF ELIGIBILITY CRITERIA

In most cases, violation of eligibility criteria is not a reason for premature withdrawal from the study. However, if, post enrolment, it is found that the patient has not been eligible at the time this must be notified to the trial CI/co-ordinator as soon as possible, and, after detailed discussion regarding the particular patient, a decision will be taken about whether they should be withdrawn from the trial.

11.0 TRIAL PROCEDURES

Home blood pressure measurements

At several points during the trial, home blood pressure measurements are recorded. These are to be measured seated after 5 minutes rest, using the non-dominant arm. Measurements will be made using an approved and validated monitor (Microlite watch BP) or equivalent. Blood pressure readings will be taken in the morning and the evening, and the timing of these should be consistent throughout the study, ideally ~ 8.0 am and 8.0 pm – or the nearest time to these that can be constant and convenient in the individual subject on 4 consecutive days. Participants will be asked to make triplicate seated readings after 5 minutes seated rest, and to record these on a pro-forma provided. All readings will also be captured automatically by the monitor.

11.1 SCREENING /ENROLMENT VISIT

Informed Consent will be taken by physician or delegated to other members of the clinical research team. This will be taken following at least 24hrs of being in receipt of the patient information sheet. Demographic information will be recorded including gender, ethnicity, age, smoker, non-smoker, height weight. Medical history of cardiac, metabolic diseases and anything PI feels is related to hyperaldosteronism. Clinical examination. Concomitant hypertension medications will be recorded via class with a start and stop date where available.

During this visit the patient will have 3 blood pressures measured in the clinic following 5 minutes seated rest. Patients will be provided with a validated blood pressure monitor to measure home blood pressure. They will receive training on how to measure and record home blood pressures in blood pressure diary provided by a member of the clinical research team. This monitor will be used for clinic and home blood pressure measurements (Please see section above on Home blood pressure measurements)

A 12 lead electrocardiogram will be recorded. Followed by blood tests including electrolytes, , bicarbonate, creatinine, high troponin sensitivity test, brain natriuretic peptide (BNP), renin mass where available, renin activity, aldosterone and FBC. A serum HCG will be measured in child bearing potential females. Patients will be provided with x2 24hr urine bottles one for electrolytes and the other for 24hr steroid profile.

Inclusion and exclusion criteria will be checked with patient and recorded onto the Ecrf. (Please see inclusion and exclusion criteria section 5.6)

Information and appointment details for 11C-metomidate PET CT scan and Adrenal Vein Procedures will be provided at this visit. The patient will then attend the PET CT scan and adrenal vein sampling procedures before next study visit , baseline visit.

NB Patients following review of PET CT scan and Adrenal Vein sampling procedure **who do not** meet the criteria for surgical intervention – adrenalectomy will attend for baseline visit, the post 2-week spironolactone /eplerenone 50mg and the post 2 week spironolactone 100mg visit. Following on from this they will have a follow-up study visit at 9-12 months. During this visit clinic blood pressures, 12 lead ECG,

Prior to baseline visit

Home blood pressure measurements will be completed by the patient with 6 measurements for 4 days recorded in blood pressure diary and brought with them for the baseline visit. Patients will also be asked to attend a cardiovascular magnetic resonance (CMR) scan before baseline visit; this will require a washout period of 6 weeks for spironolactone/eplerenone, amiloride and spironolactone/eplerenone. The CMR will be repeated again at the 6 month visit +or- 1month. Patients not having surgical removal of an adrenal gland will have a follow- up CMR 9 months following their baseline visit. Patients will be asked to arrive approximately 30 minutes before the actual scan appointment time to perform a brief assessment, complete paper work and change into a gown. A small cannula will be inserted into the patient's vein, this allows a blood sample to be taken and administration of gadolinium; it is very widely used and usually has no side effects at all; very occasionally (less than 1/100 times) it causes a temporary mild headache or nausea. The scan itself takes about forty minutes. Patients will not be included if there are any contraindications to MR imaging such as cardiac pacemakers. Patients with a contraindication to gadolinium (i.e. GFR <30 ml/min/1.73m²). No female patients will be scanned if pregnant.

11.2 BASELINE VISIT

During this visit the patient will have 3 blood pressures with heart rates measured in the clinic following 5 minutes seated rest. Home blood pressures taken from diary will be recorded onto eCRF

Bloods will be taken for electrolytes, bicarbonate, uric acid, creatinine, eGFR, high troponin sensitivity test, brain natriuretic peptide (BNP), renin mass, renin activity, aldosterone and FBC. A serum HCG will be measured in child bearing potential females, 24 hours urine steroid profile, pharmacogenetics sample, plasma and serum samples, 24 hr Urine collection for sodium and potassium

Inclusion and exclusion criteria will be re checked along with any updates on concomitant medication

During this visit the patient will be prescribed spironolactone/eplerenone 50mg once daily and have two reviews as below.

The aim is to have no longer than a 2 month run in period from screening visit to Baseline visit it will be up to PI interpretation and dependent on when 11 C Metomidate PET CT scan and AVS appointments. If a longer run in period is expected the CI should be consulted.

11.3 SPIRONOLACTONE/EPLERENONE THERAPY (Baseline Visit)

(50mg) (post 2 week baseline visit)

- Clinic BP will be measured similarly to home readings (using the same monitor) - in triplicate, after 5 minutes seated rest
- Updated medical history
- Concomitant medications
- Home blood pressure recordings for 4 days (as above)
- Electrolytes and renal function

Spirolactone/Eplerenone (100mg) Visit week 4

- Clinic BP will be measured similarly to home readings (using the same monitor) - in triplicate, after 5 minutes seated rest
- Updated medical history
- Concomitant medications
- Home blood pressure recordings for 4 days (as above)
- Electrolytes and renal function.
- Following up titration patient will have recheck of electrolytes and renal function either at clinic or as arranged with GP.

11.4 POST-SURGICAL AND NON SURGICAL FOLLOW UP SCHEDULE VISITS AT 1, 3,6,12 AND 24 MONTHs

Patients having adrenalectomy will be followed up at 1, 3, 6, 12 and 24 months. Final follow up visit will be up to two years following adrenalectomy. During these visits patients will have 3 blood pressures with heart rates measured in the clinic following 5 minutes seated rest. Home blood pressures taken from diary will be recorded onto eCRF. Bloods will be taken for electrolytes, bicarbonate, creatinine, high troponin sensitivity test, brain natriuretic peptide (BNP), renin mass, renin activity, aldosterone and FBC. A serum HCG will be measured in child bearing potential females. Patients having a baseline CMR in this group will have a repeat at 6 - 12 months following baseline CMR

For patients not requiring an adrenalectomy there will be at least one follow up visit at 9-12 following MDT. Patients having CMR in this group at baseline will have a repeat CMR at 6-12 months following MDT. Those recruited sufficiently early in the study, will have a second follow-up visit at about 2 years following MDT.

11.5 UNSCHEDULED VISITS

There will be provision in the CRF for extra visits when considered necessary by the study team. This will not be considered a deviation of the protocol if these are not completed.

11.6 PREMATURE TERMINATION OF THERAPY OR FOLLOW-UP

Patients will be **withdrawn** from the study on safety grounds if any of the following occurs and at PI discretion:

- Illness requiring hospitalisation that is likely to preclude further study participation
- Sustained Hypertension
Withdrawal will be up to PI discretion.
- Hypotension:
If the patient has symptoms consistent with hypotension and systolic BP is <110mmHg or the change in BP from previous reading is >30mmHg, and in the opinion of the investigator there is no self-limiting reason for hypotension (e.g. episode of dehydration, climatic conditions) the patient will withdraw.....

All study withdrawals will be recorded in the study conclusion page of the eCRF, indicating the date and reason for withdrawal.

It will be expected that patients return their blood pressure monitors at the end of the study or at withdrawal.

Plan of Further Treatment

Patients will be managed by their clinical physician.

12.0 ADVERSE EVENTS (AE/SAE)

definitions of adverse events

adverse event (ae) – any unfavourable and unintended sign, symptom or disease temporally associated with participation in the research project.

definition of serious adverse event

serious adverse event (sae) - an untoward occurrence that:

- a. results in death
- b. is life threatening
- c. requires hospitalisation or prolongation of existing hospitalisation and. results in persistent or significant disability or incapacity
- e. consists of a congenital anomaly or birth defect
- f. is otherwise considered medically significant by the investigator

recording and reporting of adverse events

AEs will be identified by observation and /or enquiry at study visits. AEs that do not meet criteria for seriousness will be recorded in the medical notes only. Details of SAEs will be reported to the pharmacovigilance office and followed until resolution. The relationship with the study procedures will be assessed for all SAEs. All 'related' SAEs will be forwarded to the CI for assessment of the expectedness. all 'possibly' or 'definitely' related, unexpected saes will be reported to the rec as detailed below.

All SAEs arising during the study will be reported by the principal investigator (or designee) to sponsor (pv office) as soon as reasonably practicable and in any event within 24 hours of first becoming aware of the event. any follow up information should also be reported.

SAEs should be reported using a paper SAE form (non-CTIMP) which can be downloaded from the Glasgow clinical trials unit website: www.glasgowctu.org. this should be completed and faxed to the Pharmacovigilance office. (fax no: +44 (0) 141 357 5588). a copy of the complete form should be placed in the study site file. If necessary a verbal report can be given by contacting the pharmacovigilance office on +44 (0)141 330 4870/ +44 (0)141 330 4744. this must be followed up as soon as possible with a written report.

'if a report of a "related" SAE is received at the pv office an email alert will be sent to the CI for assessment of 'expectedness' and confirmation of relationship.

Reporting to the research ethics committee (rec)

Any SAE occurring to a research participant will be reported to the main Rec (i.e. the rec that gave a favourable opinion of the study) where in the opinion of the chief investigator (CI), the event was:

- "related" – that is, it resulted from administration of any of the research procedures, and
- "unexpected" – that is, the type of event is not listed in the protocol as an expected occurrence.

reports of related and unexpected saes should be submitted to the rec within 15 days of CI becoming aware of the event, using the 'report of serious adverse event form' for Non-CTIMPS published on the national research ethics service (nres) website.

<http://www.nres.npsa.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/> the form should be completed in typescript and signed by the CI (or designee). the pv office will assist in the preparation and submission of the report. the co-ordinator of the main rec will acknowledge receipt of safety reports within 30 days.

Annual progress report

The CI is also responsible for providing an annual progress report to the rec using an nres "annual progress report form for all other research". this form is available at:

<http://www.nres.npsa.nhs.uk/applications/after-ethical-review/annual-progress-reports/> a section on the safety of participants is included in this report. the pv office will assist in the collation of the safety information required for the report. Reporting to local research and development (R&D) departments the principal investigator at each site is responsible for the provision of reports to their local R&D department per the conditions of management approval.

13.0 LABORATORY ASPECT

All blood biomarkers will be managed and reported at specific study sites were possible following their SOPs and guidelines. The 24-hour urine steroid profile will be measured and reported by the University of Birmingham as agreed by Sponsor's Technical Agreement devised by the sponsor. These will be transferred for analysis using a fit for purpose courier.

Plasma samples will require 2mls whole blood collected in EDTA spun at 300xG (RCF) and then aliquoted into 1.5ml Eppendorf tubes then frozen at 80°C. For serum sample, 3mls of blood will be drawn and when clotted the serum will be aliquoted into 1.5 Eppendorf tubes

and frozen -70°C-80°C. Both Plasma and serum samples will be transferred to Queen Mary University of London at the end of the study following the Sponsors Technical Agreement.

Following adrenalectomy tissue will be genotyped for somatic mutations in *KCNJ5*, *ATP1A1*, *ATP2B3*, *CACNA1D*, *CTNNB1* and phenotyping by histological grading, gene expression and immunohistochemistry. Routine analyses (histology, some of the immunohistochemistry) will be performed by the endocrine pathologist in the hospital where the patient has surgery, and photographs retained for central, blinded re-analysis by the study endpoints committee. If the tests are not available in the hospital where surgery was performed, tissue will be transferred to either Addenbrookes Hospital Cambridge, or to Barts Hospital, or Queen Mary University London. Non-routine analyses (e.g. genotyping, gene expression) will be performed at William Harvey Research Institute QMUL Charterhouse Square London. Using fresh-frozen, RNAlater or paraffin section prepared at the time of surgery and stored at the local hospital until batched transfer to the site of analysis.

14.0 STATISTICAL ASPECTS

Patients will receive AVS and ¹¹C metomidate PET CT in ‘pseudo-random’ order. In order to allow for patients and situations where it is logistically easier to perform one investigation before the other – e.g. when the ¹¹C-metomidate synthesis fails, and cannot be re-booked before an already scheduled AVS – we will use a minimization rather than randomisation procedure. This is a computer based programme which assigns order to each patient such that the difference in number of patients having one investigation first is minimized, but allows for the recommended order to be over-ridden. When eligibility has been confirmed, the order in which the diagnostic tests are to be performed will be obtained via the study web portal. The minimisation schedule will be stratified by study site. The minimisation schedule will be stored in a secure area of the Robertson Centre for Biostatistics network, with access restricted to those responsible for the randomisation system. Researchers at study sites will not know the order of tests until after baseline assessments have been carried out, and statisticians at the Robertson Centre will not have access to the minimisation schedule until the end of the study, when all analysis programs have been written and verified.

15.0 ENDPOINTS

15.1 PRIMARY OUTCOMES

1. Change in ARR from baseline to 6 months after surgery, or 9-12 months after MDT in patients not proceeding to surgery. (For patients whose surgery takes place less than six months prior to overall study-end, data will be used from the 3 month post-op visit, or the six-month visit will be brought forward. This qualification applies to all other reference to the six-month visit and data in this protocol.)
2. Change in SBP (mean of at least 18 measurements from 3 days home monitoring), from baseline to 6 months after treatment, or 9-12 months after MDT in patients not proceeding to surgery

15.2 SECONDARY OUTCOMES

A number of pre-specified pre-operative radiological parameters, and post-operative histological, immunohistochemical, molecular and genetic measurements will be compared between patients whose [i] ARR and [ii] blood pressure are normalized by surgical or medical treatment.

Secondary outcomes

1. Cure of hypertension, defined as the proportion of patients in whom average home blood Pressure measurements 6 months post adrenalectomy are <140/90 mmHg on no treatment.
 2. Prediction of cure of hypertension, by one or more of:
 - a) The ratio of SUVmax between tumour and normal adrenal;
 - b) Blood pressure fall on spironolactone/eplerenone (50 mg daily for 2 weeks, 100 mg daily for 2 weeks), measured as the difference in home systolic blood pressure
 - c) Post-operative analyses of the APA, to include genotyping for somatic mutations in KCNJ5, CACNA1D, ATP1A1, ATP2B3, CTNNB1 and phenotyping by histological grading (zona fasciculata versus zona glomerulosa), gene expression and immunohistochemistry.
 3. Change in home blood pressure from baseline at follow-up visits other than 6 months post-adrenalectomy.
 4. Reduction in number of antihypertensive drugs
 5. Change from baseline in blood levels of Troponin, Brain Natriuretic Peptide.
- The judgement as to which patients have met primary and secondary outcomes will be made by a critical endpoints committee meeting every 3-6 months throughout the study.

16.0 PLANNED METHODS OF ANALYSIS

The planned study analyses will be detailed in the study-specific Statistical Analysis Plan (SAP), which will be finalised in advance of study closure.

The primary outcomes will be analysed in a hierarchical manner:

1. Compare changes in ARR between patients who have surgery and those who continue medical treatment
2. Compare cure rates (home SBP < 135 mmHg) between patients who have surgery and those who continue medical treatment
3. Compare ARR in patients who have surgery and those who continue medical treatment
4. Compare cure rates (home SBP \geq 10% lower than pre-spironolactone/eplerenone, i.e. baseline) amongst patients who have surgery but have discordant AVS and PET-CT results
5. Compare cure rates (home SBP < 135 mmHg on no antihypertensive treatment) amongst patients who have surgery but have discordant AVS and PET-CT results

Safety Evaluation

Safety evaluation will include all patients in the Safety Population, and will be descriptive in nature.

16.1 INTERIM ANALYSIS

There are no planned interim analyses.

16.2 FINAL ANALYSIS

The final study analysis, as detailed in the SAP will be carried out after study closure and the study databases have been finalised and locked.

16.3 SAMPLE CALCULATION

The calculations on sample size are based on our stated intention that AVS will only be performed in centres whose robust audit data indicate a bilateral cannulation rate of $\geq 75\%$, as the testing of the hypothesis will have maximum clinical value if ^{11}C metomidate scanning is compared with current best practice AVS. It also assumes that 100% of metomidate scans will provide a technically satisfactory result (we consider this to be reasonable, based on the Cambridge experience since the investigation was first introduced in May 2009).

The design of the study (and therefore the statistical analysis) presupposes that there will be a group of patients for whom the results from metomidate scanning and AVS will differ, but that the former is correct more often and that this difference is statistically significant. Given the results of the proof-of-concept study, it is inevitably the case that there will be a large group of patients for whom the two tests are concordant. The different scenarios of concordant/discordant, unilateral/bilateral, together with their estimated frequencies, are shown in Appendix, and it is these figures that have been used by the Clinical Trials Unit in Glasgow as the model for the sample size calculation and proposed analysis.

Recruitment of 140 patients across 3 centres over 3 years ($<1/\text{centre/month}$), with an estimated 70 proceeding to adrenalectomy, permits 90% power at $\alpha=0.01$ of detecting superiority of PET CT over AVS. Based on the current size of referral practices at each centre, we are confident of meeting the recruitment target.

There will be a sub-study of 6 patients who will have a ^{11}C metomidate PET CT scan before and following spironolactone/eplerenone therapy. In our previous study, the uptake of metomidate into tumour was 60% greater than contralateral normal adrenal (mean(SD) = 21.7(8.0) vs 13.8 (3.0)). The study of six patients on two occasions will give us 90% power to detect just 30% increase in normal adrenal uptake, even if there is no parallel increase in tumour uptake of metomidate ($\alpha=0.05$, one-sample test).

17.0 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

17.1 ETHICS COMMITTEE

The trial can only start after full and written approval of the protocol and all addenda has been obtained from the local Independent Ethics Committee. The Independent Ethics Committee must be informed of all subsequent, substantial protocol amendments issued by the sponsor. The investigator will provide reports to the Ethics Committee at intervals stipulated in the Ethics Committee guidelines. The MATCH study has been reviewed by the Dulwich Research Ethics Committee.

17.2 DATA MONITORING AND ETHICS COMMITTEE (DMEC):

This will be established at the outset of the study to consider ‘stopping rules’, and will meet once a year thereafter. We plan to invite Prof Peter Sever or Prof Neil Poulter from Imperial College London, who are both experienced at conducting clinical trials in the hypertension field, to chair the DMEC. However, we have not yet approached them, or other possible external members of the TSC or DMEC, so as not to cause any conflict of interest if they are approached by NIHR as reviewers of this application.

17.3 CRITICAL END POINTS COMMITTEE

This will consist of two physicians (Endocrinologist and Hypertension specialist), a Pathologist and a Clinical Biochemist. They will be independent of those involved in the patients’ care, or the pre-operative assessments, and blinded to the results of the imaging investigations. This committee will meet every 3-6 months to review anonymised trial data.

17.4 THE STEERING COMMITTEE

Trial Steering Committee (TSC): This will comprise four independent members, including the Chair, and the three lead investigators Prof Brown, Prof Drake and Dr Gurnell); observers from the EME Programme will be invited to attend in person or by teleconference. Professor Fiona Gilbert, Head of the Academic Department of Radiology in Cambridge, has accepted to serve as Chairperson of the TSC if this is acceptable to EME. External members will be approached as outlined below (see DMEC). The full membership will be balanced between clinicians with clinical trials and endocrine experience, and radiologists. A patients’ representative has been identified and will be included. The TSC will meet twice yearly.

18.0 DATA HANDLING

The Robertson Centre for Biostatistics at Glasgow University will act as the Data Centre for the trial. It will be responsible for the development of a web-based electronic case report form (eCRF) system for recording trial data at the study sites.

The eCRF will include sections relating to each trial contact with the patient.

18.1 DATA Collection

Study data will be recorded via remote data entry into a web-based electronic case report form (eCRF) developed for the study. A manual for eCRF use will be provided for all trial sites. Data entry into the eCRF will be performed either by the investigator or documented designee. The investigator will confirm electronically the completeness and correctness of eCRF completion.

A reason will be supplied for any subsequent changes made to submitted eCRF data.

18.2 DATA COLLECTION AND ECRF

A Patient Identification List will be created containing personal data such as the name, gender and date of birth of all study subjects, together with their assigned study number. This list does not form part of the eCRF, and will be stored securely at the study site. This is to enable later identification of the study subjects. However, the eCRF data will be anonymous, identifying study subjects by only their assigned study number.

Section 6 details the various data recorded during the course of the trial. These data will all be entered directly into the eCRF, with the exception of the following, which will be recorded electronically and transmitted separately to the Data Centre.

- Screening visit 12-lead ECG result

18.3 DATA MANAGEMENT

Whenever possible, data will be entered into the eCRF directly online. If this is not possible, data will be entered and stored in individual laptops/PCs, or recorded onto paper until internet access is possible.

The Robertson Centre for Biostatistics, University of Glasgow is responsible for all data management for the trial data. Data management will be in accordance with the Robertson Centre's SOPs.

18.4 RECORD RETENTION

ICH/GCP guidelines require that the investigator or the institution maintains all Case Report Forms and all source documents that support the data collected from each participant plus all trial documentation. Measures will be taken to prevent accidental or premature destruction of these documents. Essential documents must be retained for at least 20 years.. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained. If the responsible investigator retires or leaves the institution responsibility for the documentation must be transferred to a person who will accept their custody.

18.5 RECORD ARCHIVAL

The study data and documentation will be archived in accordance with the relevant regulatory requirements and site SOPs.

19.0 QUALITY CONTROL AND QUALITY ASSURANCE

19.1 DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS

According to GCP, the trial investigators will permit authorised third parties access to the trial site and medical records relating to trial subjects. This will include, but not necessarily be restricted to, access for trial-related monitoring, audits, Ethics Committee review and regulatory inspections.

19.2 MONITORING

Monitoring of centre may be undertaken by a trained study monitor or monitors, to verify the completeness and correctness of the study documentation.

19.3 AUDITS

The sponsor reserves the right to audit trial sites, subject to giving a suitable period of notice (minimum period of notice 10 working days).

19.4 INSPECTIONS

Any study site may be audited by the relevant legal/ regulatory authorities.

20.0 DATA PROTECTION

Study data will be protected in accordance with the UK data protection legislation. All study data held electronically from participating study sites will be anonymised. Data will only be identified by the subjects unique study identifier.

The Patient Identification List (linking study number to patient identity) will be stored securely at the study site.

21.0 ADMINISTRATIVE AGREEMENTS AND PROTOCOL ADHERENCE

This trial will be conducted in accordance with the declaration of Helsinki including all revisions.

Protocol violations comprise any deviation from the procedures defined in the protocol, any missed assessments, and non-compliance with study medication. The investigator should make considerable effort to ensure protocol adherence, or to correct any protocol violations that occur.

All protocol violations should be documented, and any major protocol violations should be reported immediately to the study co-ordinator.

If a protocol deviation is required in order to eliminate an immediate hazard to a study participant, this should be documented, indicating the form of deviation, and the reason that this was necessary.

21.1 PROTOCOL AMENDMENTS

Neither the investigators nor any personnel involved in the study conduct may alter the study protocol. Protocol amendments will only be made under exceptional circumstances, and only with full agreement of the study Executive Committee. Any protocol amendments agreed will be recorded in writing. All protocol amendments will be notified to all study sites and involved study personnel.

21.2 FUNDING

The MATCH study is supported by funding from the NIHR EME project number **EME Project number: 14/145/09**

21.3 INSURANCE

Queen Mary University of London is sponsoring this study and has arranged for suitable indemnity cover to be in place. Cambridge University as the manufacturer of 11-C metomidate will insure the product. Cambridge University Hospitals NHS Foundation Trust at which the 11-C metomidate PET CT scan is to be undertaken will provide suitable indemnity cover for the procedure.

21.4 PUBLICATION POLICY

Publications will be supervised by the British Hypertension Society Research Committee. This committee will determine the authorship of each paper using CONSORT guidelines.

21.5 CASE PAYMENTS

Investigators will only be reimbursed for any study-related expenses.

a) CONFIRMATION OF THE FINAL PROTOCOL

The signatories confirm that they agree to conduct their study-related responsibilities in accordance with local law, the declaration of Helsinki including all revisions, and the study protocol

Chief investigator

(Professor M J Brown)

Signature

Date

b) PROTOCOL AGREEMENT

The signatory declares that:

- he/she will conduct his/her study responsibilities in accordance with law, the declaration of Helsinki including all revisions, and the study protocol.
- he/she has read the study protocol and agrees to it in its entirety

Principal investigator

NAME (block capitals): _____

Signature: _____

Date: _____

Affiliation and address: _____

c) APPENDICES

a. Abbreviations

AE	Adverse event
ACTH	Adrenal
ARB	Angiotensin receptor blocker
ARR	Aldosterone renin ratio
ACEI	Angiotensin converting enzyme inhibitor
AVS	Adrenal Vein Sampling
BAH	Bilateral adrenal Hyperplasia
BP	Blood pressure
BHS	British Hypertension Society
BHF	British Heart Foundation
CCB	Calcium Channel Blocker
eCRF	electronic Case Report/Record Form
DBP	Diastolic blood pressure
ECG	Electrocardiogram
HCG	Human chorionic gonadotrophin
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	Interactive voice response system
IV	Intravenous
MDT	Multidisciplinary Team
MR	Mineralocorticoid receptor
NICE	National Institute for Clinical Excellence
o.d.	Omnia die/once a day
PI	Principal Investigator
PET	Positron electron tomography
PH	Primary hyperaldosteronism
PHA	Primary Hyperaldosteronism
p.o.	Per os/by mouth/orally
SAE	Serious adverse event
SBP	Systolic blood pressure
SUSAR	Suspected unexpected serious adverse drug reaction

b. PHARMACOGENETIC RESEARCH

DNA repositories from studies so patients may gain early benefits from the rapid advances in DNA technology in tailoring therapy or reducing side effects. It is already possible to study more than a million markers or single nucleotide polymorphisms across the genome. By the time our study is finished, it may be financially as well as technically feasible to sequence every gene in the genome.

i. Study Population and Assessment

Prior to subject participation, specific informed consent for this procedure will be signed by the patient. This research is voluntary and if a patient refuses pharmacogenetic participation they will not be excluded from the clinical study.

A 10ml sample of whole blood will be taken into an EDTA tube following informed consent. Although it is best to take the sample at the beginning of the study, it may be taken any time throughout the study. The tube label will identify subjects only by study number. No personal details will be recorded on the tube, and only designated study members will be able to link DNA analyses to the anonymised clinical data collected during the study. Samples will be stored securely at study sites before shipment to St Bartholomew's London and other sites will be invited during progress of study if required and ethics will be updated .

The named study team members at each site will hold a link between study number and patient name, as is required to permit monitoring and audit of patient records. This link will be used if a subject wishes to withdraw their sample from analysis, subjects can request destruction of their sample and any data extracted from it and pharmacogenetic consent withdrawal form will be completed and signed by the patient. It will record confirmation that the sample has been destroyed following site destruction Trust policy..

Pharmacogenetic research is likely to continue following completion of the clinical study. As is standard for most large-scale genetic studies, samples will be held indefinitely in view of the large amount of potential data they contain and the length of time it might take to mine this data. As the potential uses of these samples cannot be fully predicted at this point, the Informed Consent Document stipulates that samples might also be used for research purposes unrelated to the focus of this clinical study.

If a subject withdraws from the study other than not attending follow up and has not asked for pharmacogenetic destruction, research will continue as stated in their informed consent.

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