Trial Procedures and Assessments

Investigator Meeting

1st May 2015, University of Birmingham Medical School

BIRMINGHAM CLINICAL TRIALS UNIT

UNIVERSITY OF BIRMINGHAM

Hull and East Yorkshire Hospitals NHS Trust

NHS

Trial Procedures and Assessments

- Site set-up
- Patient identification
- Randomisation
- Visit schedule
- Trial assessments
  - Trial Samples
  - Quality of Life questionnaire
  - 6-minute walk test
- Pharmacy arrangements

Site set-up

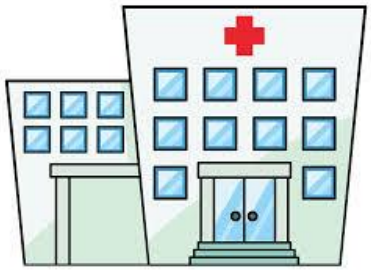
Please send a copy of the following documents to BCTU:

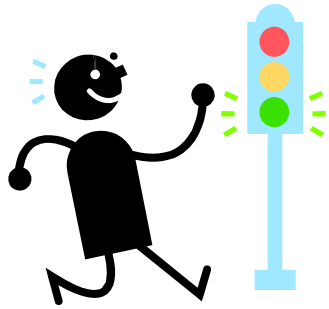
Practical Arrangements Form	BCTU provide form. Complete page 3 only or complete fully if BCTU to complete SSI on your behalf.
Localised study documents	Please send your letter head to BCTU and we will adapt the documents for you.
CVs, GCP certificates and honorary staff	Up to date documents needed for all staff working on STOP-ACEi.
SSI form	BCTU will transfer to you via IRAS or we can complete the SSI form for you if you fully complete the PAF.
Contract	Complete the contract details form and BCTU will adapt the template contract for you.
NHS permission	Let us know if we can help with local set-up processes. Please send us a copy of your approvals letter.
Delegation log	To confirm that tasks are appropriately delegated before you start recruitment. Updated throughout the trial.

Site set-up – Site Initiation Visit

- By teleconference
- Arranged when you are ready to start trial activity
- Afterwards:
  - SIV Report
  - Resolve issues
  - Sponsor green light

Site set-up – Sponsor ‘green light’





Hull and East Yorkshire Hospitals NHS Trust

Site

Prepare SSI or PAF
R&D approval letter
Signed contract
CVs
GCP certificates
Honorary contracts
Letterhead or localised docs
Sign delegation log

BCTU

Send ISF
Conduct SIV
Prepare SIV report
Resolve any issues
Apply for green light

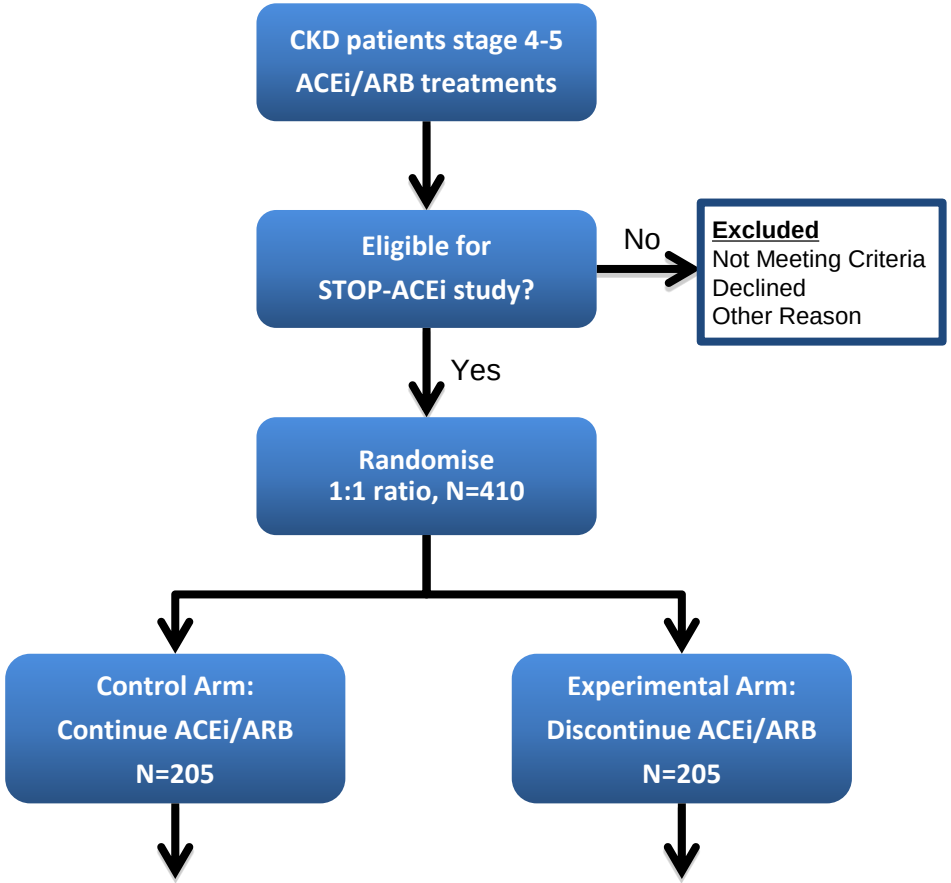
Sponsor

RG Checks
Give green light

Trial schema

2 years recruitment

3 years follow-up



3 Year Follow-Up

3-monthly visits	- routine tests (eGFR, FBC, BCP, urinary PCR), BP, documentation of ESA dose, adverse events, compliance and changes in medication
Extra tests at annual visits	- QOL questionnaire, weight and BMI, 6-minute walk test, ECG, and bloods for C-reactive protein, cystatin-C, NT-proBNP, ACE/renin levels and biomarkers

Eligibility

Main Inclusion criteria	Main Exclusion criteria
≥18 years	Uncontrolled BP (≤160/90 mmHg or more than 5 agents to control BP)
Advanced (stage 4 or 5) CKD	On dialysis or had transplant
Pre-dialysis, with no previous transplant	Unsuitable for trial due to prognosis to prognosis/projected survival of less that 12 months
Progressive deterioration in renal function (fall in eGFR of >2ml/min/year)	MI or stoke in last 3 months
On ACEi and/or ARB ≥6 months with at least 25% of the maximum recommended daily dose on the day of consent	Immune-mediated renal disease that requires disease-specific treatment
Controlled BP (≤160/90 mmHg)	Participation in interventional research in last 6 weeks
3 months specialist renal follow-up	Unable to comply with trial schedule and follow-up
Written informed consent	Unable to provide informed consent

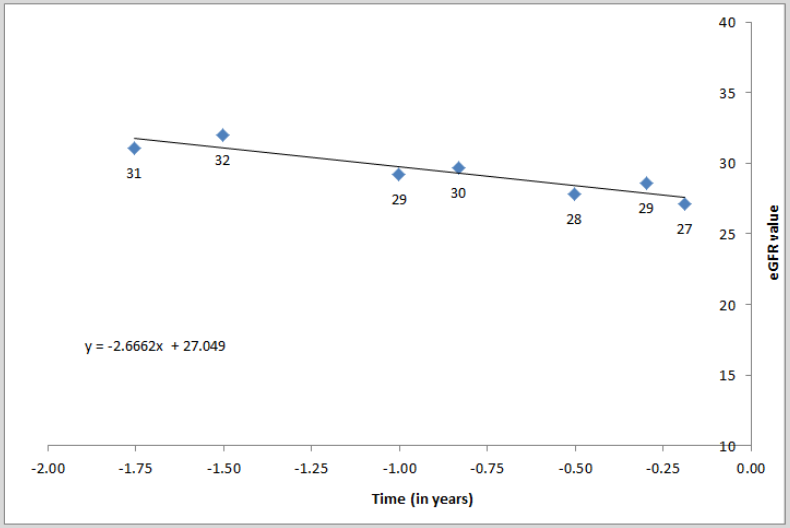
- More details in the Protocol

Eligibility - eGFR decline

Progressive deterioration in renal function (fall in eGFR of >2ml/min/year over previous 24 months) as measured by linear regression analysis.

Male/Female	Male
Is ethnicity black?	No
Date of Birth:	01/01/1949
Screening date:	01/12/2013
Rate of decline:	-2.67 mL/min/year
Is patient eligible?	**ELIGIBLE**

Date of eGFR	Serum creatinine
01/03/2012	200
01/06/2012	195
01/12/2012	211
01/02/2013	208
01/06/2013	220
15/08/2013	215
23/09/2013	225



Patient Recruitment

Identify potential participants	
Against inclusion/exclusion criteria	From medical records

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Invite potential participants to take part	
1-2 weeks before next clinic appointment	REC-approved Letter to Accompany PIS
Record details of all participants considered for STOP-ACEi in the approach log	REC-approved Participant Information Sheet

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Discuss participation in STOP-ACEi	
At next clinic appointment	Discuss risks/benefits - equipoise

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Informed Consent Process	
Appropriately trained medically qualified staff	Optional consents

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Final eligibility check
Appropriately trained medically qualified staff

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RANDOMISE

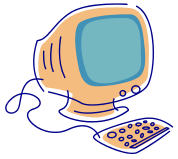
Randomisation

9am – 5pm, Mon-Fri
0800 953 0274

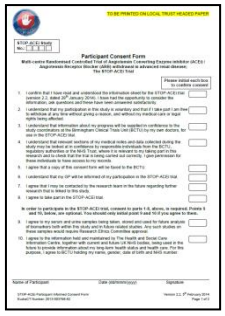
Collect info on
Rand. Notepad

Randomise

Confirmation
e-mail



24hrs / 7 days
www.trials.bham.ac.uk.stopacei



Complete trial
ID on ICF

Fax the completed
ICF to BCTU
0121 415 9135

BCTU will perform
checks

Trial visits and procedures

Trial visit number		1	Phone call	2	3	4	5	6	7	8	9	10	11	12	13
Visit month (± 2 weeks)	Screening	Baseline		3	6	9	12	15	18	21	24	27	30	33	36
Inclusion and exclusion criteria	Y	Y													
Informed consent / randomisation		Y													
Demographics: Date of birth, gender, ethnicity		Y													
Medical history including cardiovascular co-morbidity & CKD aetiology		Y													
Smoking status / alcohol intake		Y													
Height		Y													
Weight / BMI		Y					Y				Y				Y
Blood pressure		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Record ESA dose		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Record data from cardiac echo †		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Changes to anti-hypertensive / con-medication ‡		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Compliance with the trial treatment allocation		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Adverse event documentation		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Routine tests														
eGFR and BCP*		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
FBC**		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Urinary PCR by early morning spot urine		Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
CRP		Y					Y				Y				Y
	Additional tests														
Six minute walk test		Y					Y				Y				Y
KDQOL-SF™ v1.3 Questionnaire		Y					Y				Y				Y
12 Lead ECG		Y					Y				Y				Y
Cystatin-C / NT proBNP / ACE / Renin		Y					Y				Y				Y
Serum and urine samples for biomarker analysis ***		Y					Y								Y

Trial samples

	What will be tested	Where analysed	When samples taken
Routine tests	Biochemical profile eGFR Full blood count Urinary PCR CRP	Locally, at your site.	Baseline Every 3-monthly trial visit (CRP taken annually)
Standard Trial Samples	Cystatin-C NT-proBNP ACE Renin levels	Centrally, at Hull lab	Baseline, Month 12, Month 24, Month 36
Optional Biomarker Samples	unknown biomarkers in future analysis	Centrally, at Hull lab	Baseline, Month 12, Month 36

- See protocol for details of BCP and FBC
- Centrally analysed samples
  - Prepare according to trial guide in site file
  - Store at -80°C until sent to central lab in Hull
  - BCTU to arrange transport approx. annually

Trial samples

Preparing the tubes and labels

Please prepare the tubes and labels before taking any samples to avoid confusion. You will not be able to tell the difference between types of sample once they are separated so the tubes need to be labelled first. We recommend that you do this before the patient arrives.

- Please use the provided screw-cap bottles.
- You will need 4 x bottles for the standard trial samples and 6 x bottles for biomarker serum samples (= 10 bottles in total) for each visit.
- Label all bottles with the participant trial ID number, the trial visit and sample type (i.e. plasma, serum or urine) using the stickers provided.
- Put the label on the tube vertically so that the sample is visible from top to bottom on the other side of the tube.

Please do not write the hospital number or patient name on the bottles to prevent sharing patient identifiable information

- Use yellow caps for the serum samples and purple caps for the plasma samples to match the blood collection tubes. Use clear caps for urine samples

PREP TUBES

10 x 

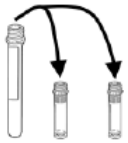
STOP-ACEi ID: __ __ __ __

Visit: __ __ Type: __

Trial samples

Sample Preparation

NB. Renin samples must be prepared and frozen within 1 hour of venepuncture.

Blood samples only. After taking the samples, leave them to stand upright at room temperature for 10-20 min, but no longer than 2 hours, to allow clotting.		CLOT
Blood samples only. Centrifuge samples at 3000 rpm (~1500*g*) for 5 mins.		SPIN
Blood and urine samples. Aliquot the samples into the *labelled* tubes. Tubes should be ¾ full (approx. 1 mL) if possible. Cap with the appropriate caps (yellow = serum, purple = plasma, clear = urine).		ALIQUOT
Blood and urine samples. Freeze the samples upright at -80°C as soon as possible after aliquoting. **Update the freezer log**.		FREEZE

KDQoL-SF™ Questionnaire

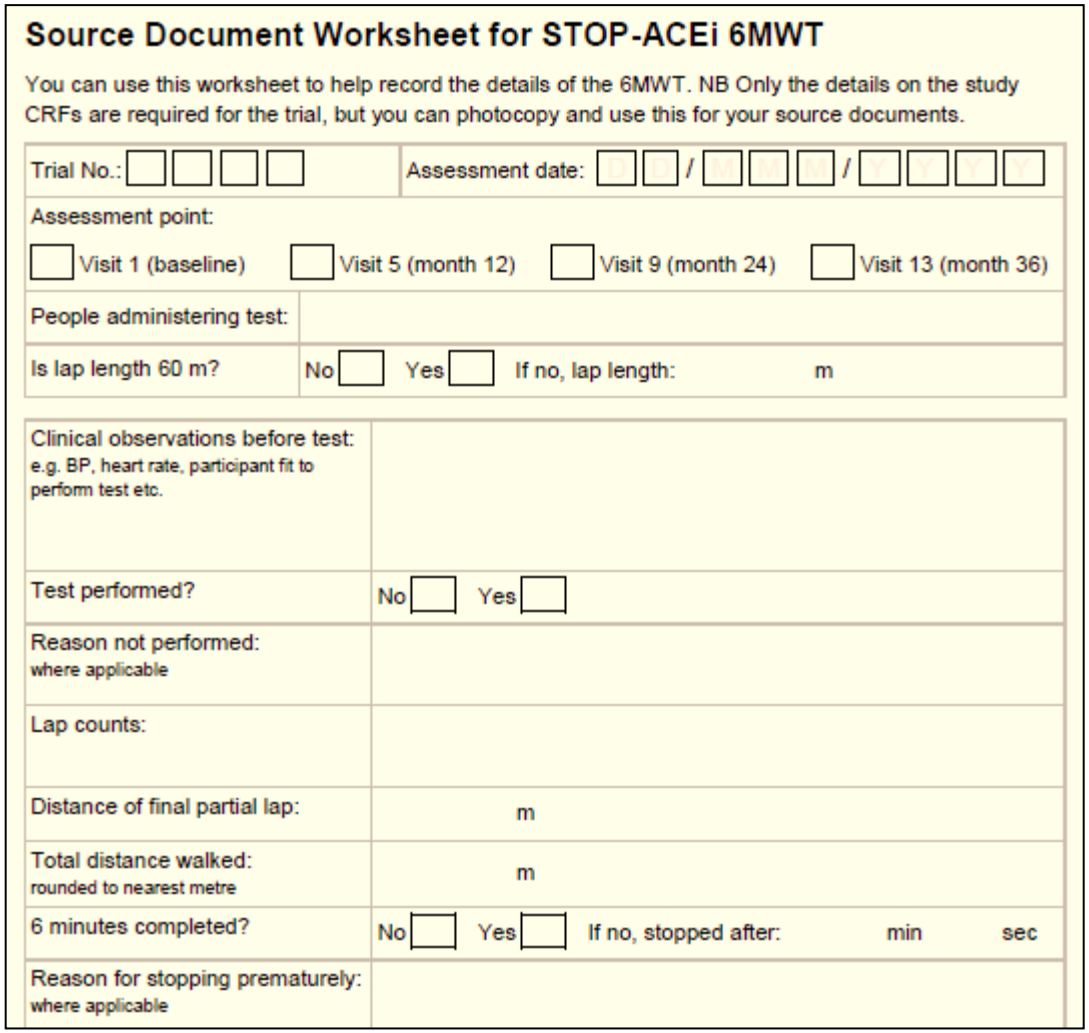
- Importance for the trial
  - Can't assess effect of trial treatment on patient wellbeing without input from the patient
  - Disease-specific
- Completed by participant
- Ideally alone to prevent influence
- RN can check for completeness or causes for concern
- Consider timing – before uncomfortable assessments or randomisation
- Allow time - While patient is waiting to be seen

Six-minute walk test

- Importance for the trial
  - Test the effect of the trial intervention on physical function
- Follow the trial guide (based on validated ATS guide)
- Identify a space
  - Measured
  - Consistently available
  - No obstructions
- Standardised script to follow
- Consider safety
- Consider timing – patient at rest for ECG and BP

Six-minute walk test

- There's a worksheet at the back of the trial guide.



Source Document Worksheet for STOP-ACEi 6MWT

You can use this worksheet to help record the details of the 6MWT. NB Only the details on the study CRFs are required for the trial, but you can photocopy and use this for your source documents.

Trial No.: ☐☐☐☐	Assessment date: ☐☐/☐☐☐/☐☐☐☐
Assessment point: ☐ Visit 1 (baseline) ☐ Visit 5 (month 12) ☐ Visit 9 (month 24) ☐ Visit 13 (month 36)	
People administering test:	
Is lap length 60 m?	No ☐ Yes ☐ If no, lap length: m

Clinical observations before test: e.g. BP, heart rate, participant fit to perform test etc.	
Test performed?	No ☐ Yes ☐
Reason not performed: where applicable	
Lap counts:	
Distance of final partial lap:	m
Total distance walked: rounded to nearest metre	m
6 minutes completed?	No ☐ Yes ☐ If no, stopped after: min sec
Reason for stopping prematurely: where applicable	

Pharmacy considerations

- Choice of drugs used is at clinician's discretion
  - ACEi/ARB
  - Other antihypertensives
- Standard Pharmacy stocks used
- No need for additional pharmacy management
  - Accountability logs ✗
  - Study-specific prescription ✗
  - Normal checks and clinical governance ✓

Casenote documentation

- See guidelines in ISF
- When patient is approached
  - Name of trial
  - Date approached about study or PIS given
  - Copy of PIS
  - Date of consent + record of discussion to show patient is ‘informed’
  - Copy of signed consent form
  - Trial ID number
  - Arm they’ve been randomised to
  - Name of PI to contact about the study if any issues
- For each visit
  - Date and study visit number e.g. STOP-ACEi baseline visit
  - Any clinically relevant information e.g. medical history, changes to treatment/prescriptions, results of any medically relevant trial assessments
  - For AEs, a brief description of the event inc. start/stop dates and results of any clinically pertinent assessments made relating to the AE