Progress Review and Trial Management

Investigator Meetings

1st and 2nd September 2016 – London and Leeds

UNIVERSITY OF BIRMINGHAM | BCTU Birmingham Clinical Trials Unit | Hull and East Yorkshire Hospitals NHS Trust | NHS

Outline

- Year in review
- Patient identification, recruitment and randomisation
- Trial Procedures
- Proposed protocol changes

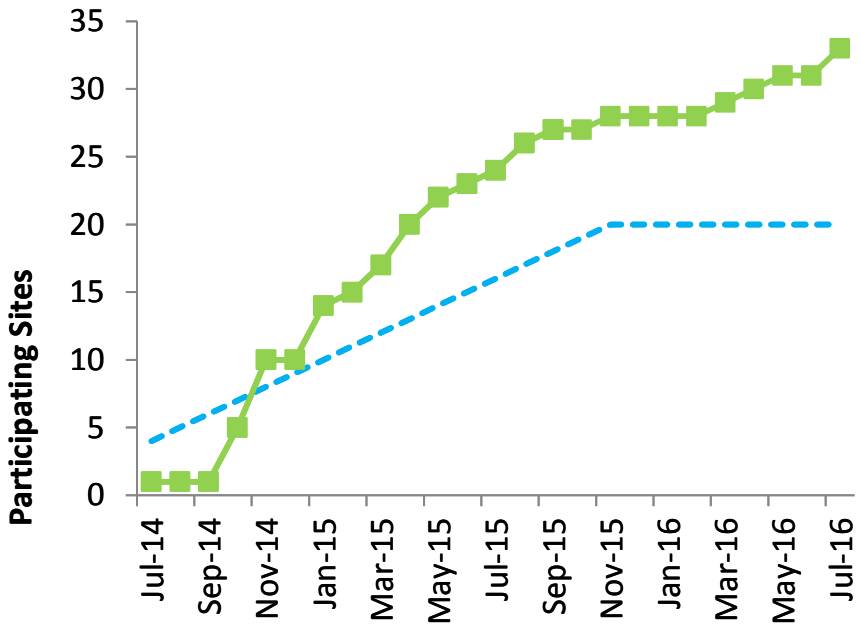
Sites

- At our last meeting…

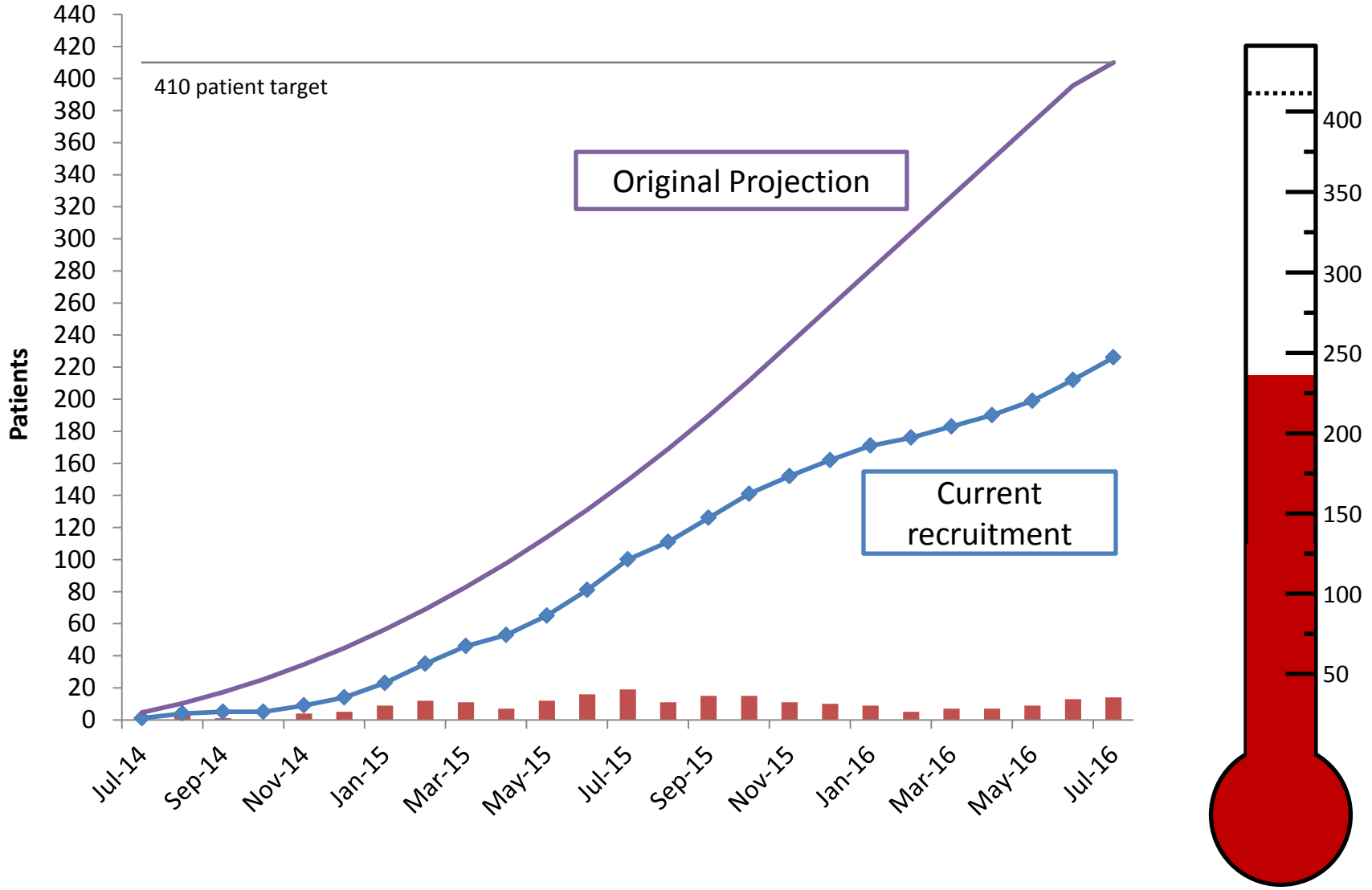
  20 sites open

- Now…

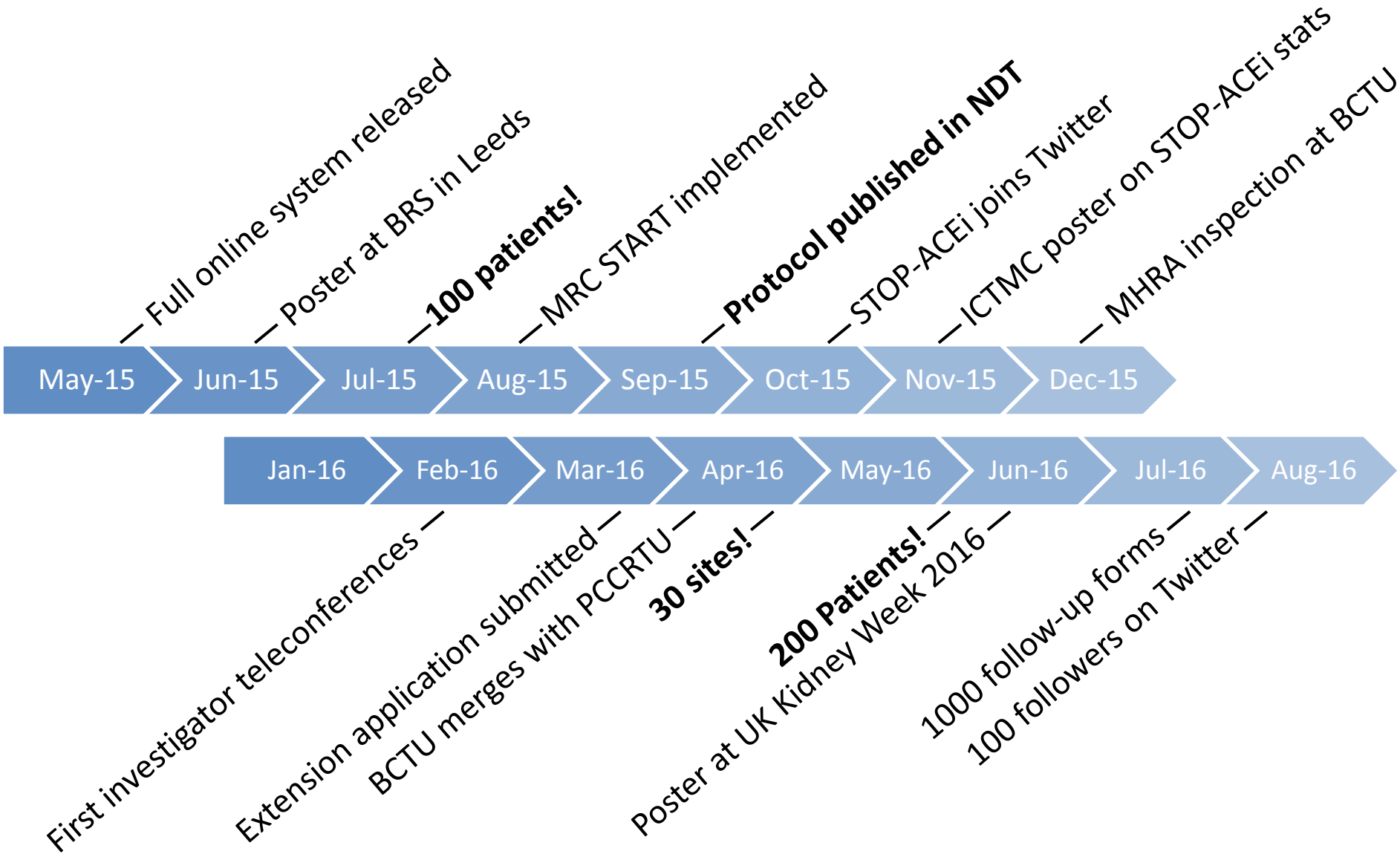
  33 sites open



Recruitment



Since our last meeting…



Since our last meeting…

Nephrol Dial Transplant (2016) 31: 255–261
doi: 10.1093/ndt/gfv346
Advance Access publication 30 September 2015

Multicentre randomized controlled trial of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker withdrawal in advanced renal disease: the STOP-ACEi trial

Sunil Bhandari[1,2], Natalie Ives[3], Elizabeth A. Brettell[3], Marie Valente[3], Paul Cockwell[4], Peter S. Topham[5], John G. Cleland[6], Arif Khwaja[7] and Meguid El Nahas[7]

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Nephrol Dial Transplant (2016) 31: 171–173
doi: 10.1093/ndt/gfv351
Advance Access publication 6 October 2015

ndt
Nephrology Dialysis Transplantation

In Focus

'To block or not to block'; whether to continue renin–angiotensin–aldosterone system blockade in advanced chronic kidney disease

Marit D. Solbu[1,2] and Alan G. Jardine[1]

[1]BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK and [2]University Hospital of North Norway, Tromsø, Norway

Correspondence and offprint requests to: Alan G. Jardine; E-mail: alan.jardine@glasgow.ac.uk

"there is considerable uncertainty about the use, and effects, of blockade of the RAAS, and specifically the possible benefits or adverse consequences of withdrawal of ACEi and ARBs, in patients with CKD stage 4 and 5"

"It is an important issue with clinically relevant goals, which will have an immediate impact on the way we manage patients with common renal conditions"

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- Trial Procedures
- Proposed protocol changes

Patient Recruitment

Identify potential participants	
Against inclusion/exclusion criteria	From medical records

↓

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

↓

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

↓

Informed Consent Process	
Appropriately trained medically qualified staff	Optional consents

↓

Final eligibility check
Appropriately trained medically qualified staff

↓

RANDOMISE

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
Progressive deterioration in renal function (fall in eGFR of >2ml/min/year, confirmed using the eGFR decline calculator provided)	Unsuitable for trial due to prognosis/projected survival of less that 12 months
Pre-dialysis, with no previous transplant	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

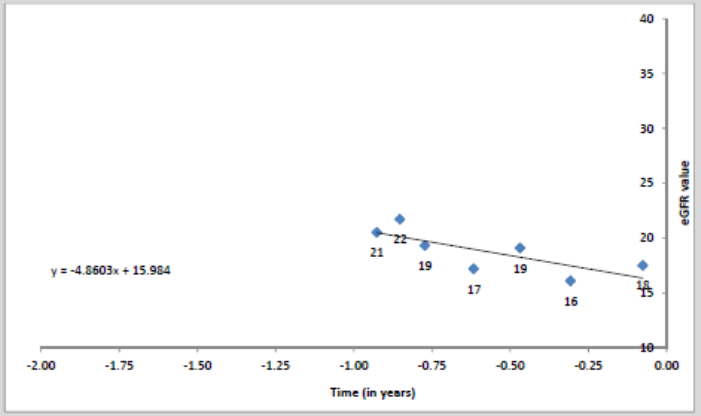
- More details in the Protocol

Eligibility - eGFR decline

- Fall in eGFR of >2ml/min/year measured by linear regression.
- 1 reading within the last 3 months
- 3 readings per year needed for accuracy
- All readings within last 24 months
- No need to include all results, but omissions should be clinically justifiable
- Patient must be clinically in decline and pass the decline test

Male/Female	Female
Is ethnicity black?	No
Date of Birth:	12/05/1945
Screening date:	21/08/2016
Rate of decline:	-4.86 mL/min/year
Is patient eligible?	ELIGIBLE

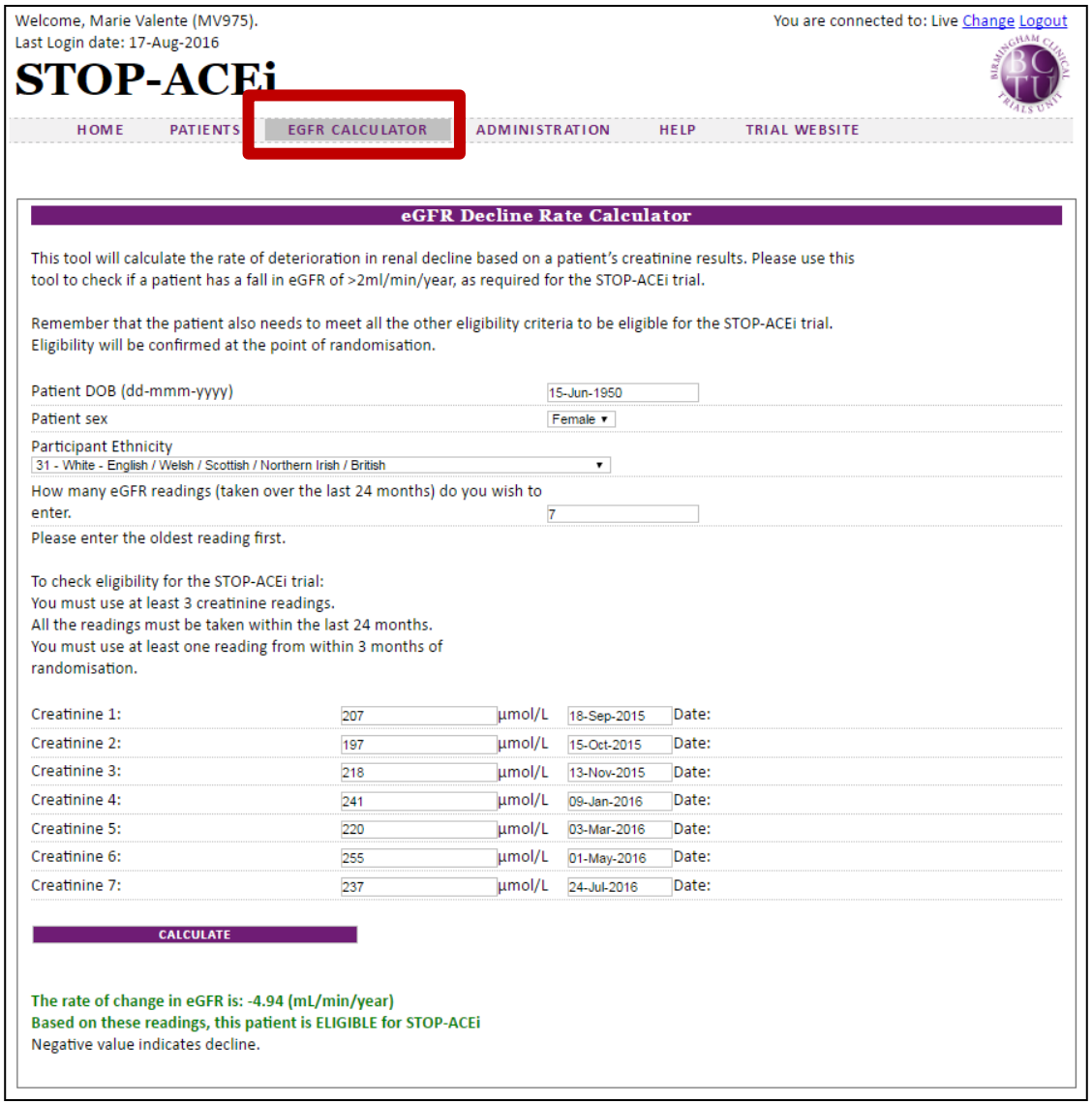
Date of result	Serum creatinine
18/09/2015	207
15/10/2015	197
13/11/2015	218
09/01/2016	241
03/03/2016	220
01/05/2016	255
24/07/2016	237



Please see the trial protocol for full details of the eligibility requirement for deteriorating renal function

- Number of results within the last 3 months = 1
- Results older than 2 years or future dates will be highlighted in red

Eligibility - eGFR decline



Welcome, Marie Valente (MV975).
Last Login date: 17-Aug-2016

You are connected to: Live Change Logout

STOP-ACEi

HOME | PATIENTS | EGFR CALCULATOR | ADMINISTRATION | HELP | TRIAL WEBSITE

eGFR Decline Rate Calculator

This tool will calculate the rate of deterioration in renal decline based on a patient's creatinine results. Please use this tool to check if a patient has a fall in eGFR of >2ml/min/year, as required for the STOP-ACEi trial.

Remember that the patient also needs to meet all the other eligibility criteria to be eligible for the STOP-ACEi trial. Eligibility will be confirmed at the point of randomisation.

Patient DOB (dd-mmm-yyyy): 15-Jun-1950

Patient sex: Female

Participant Ethnicity: 31 - White - English / Welsh / Scottish / Northern Irish / British

How many eGFR readings (taken over the last 24 months) do you wish to enter.: 7

Please enter the oldest reading first.

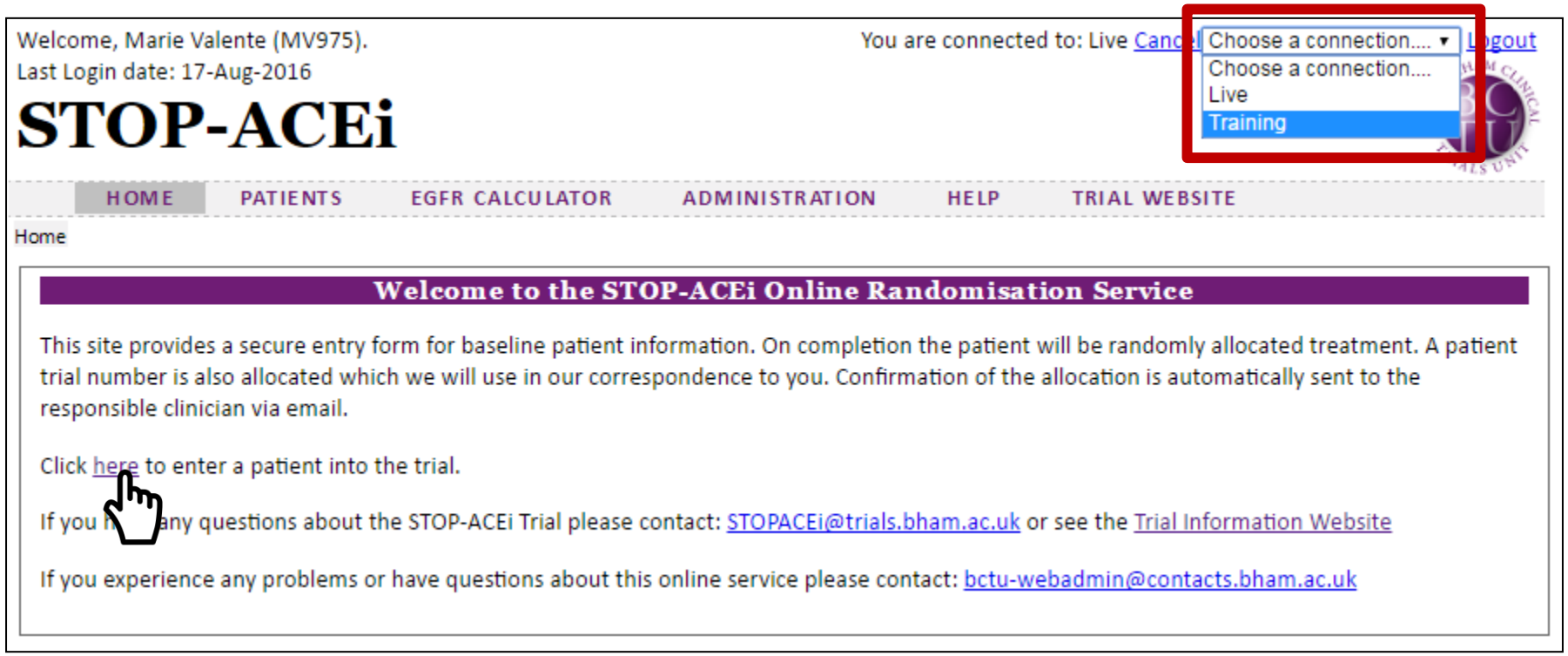
To check eligibility for the STOP-ACEi trial:
You must use at least 3 creatinine readings.
All the readings must be taken within the last 24 months.
You must use at least one reading from within 3 months of randomisation.

Creatinine 1:	207	µmol/L	18-Sep-2015	Date:
Creatinine 2:	197	µmol/L	15-Oct-2015	Date:
Creatinine 3:	218	µmol/L	13-Nov-2015	Date:
Creatinine 4:	241	µmol/L	09-Jan-2016	Date:
Creatinine 5:	220	µmol/L	03-Mar-2016	Date:
Creatinine 6:	255	µmol/L	01-May-2016	Date:
Creatinine 7:	237	µmol/L	24-Jul-2016	Date:

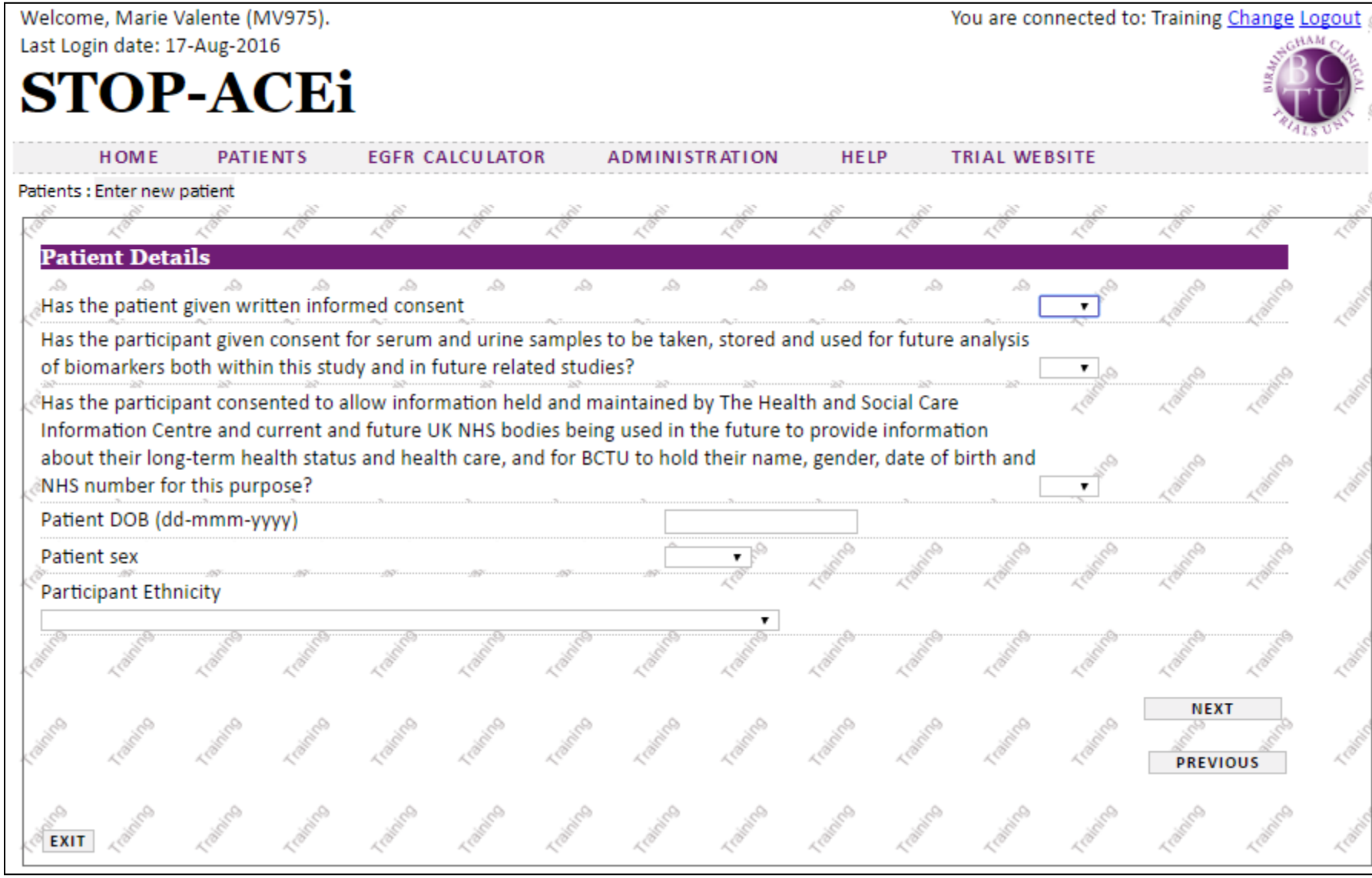
CALCULATE

The rate of change in eGFR is: -4.94 (mL/min/year)
Based on these readings, this patient is ELIGIBLE for STOP-ACEi
Negative value indicates decline.

Eligibility – doing a 'dry run'



Eligibility – doing a ‘dry run’



Eligibility – Proposed changes

- Risk of CKD progression demonstrated by…
  - Fall in eGFR of >2ml/min/year measured by linear regression
  - OR presence of proteinuria

- Requirement for at least 3 months of renal follow-up will be removed

- Improvements are planned for the patient information sheets

Patient Recruitment

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Against inclusion/exclusion criteria	From medical records

↓

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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

↓

Final eligibility check
Appropriately trained medically qualified staff

↓

RANDOMISE

MRC START sub-study

Hull and East Yorkshire Hospitals NHS Trust

PARTICIPANT INVITATION AND INFORMATION SHEET

Trial Title:
Multi-centre Randomised Controlled Trial of Angiotensin Converting Enzyme inhibitor (ACEi) / Angiotensin Receptor Blocker (ARB) withdrawal in advanced renal disease; The STOP-ACEi Trial.

Invitation to take part in this research study

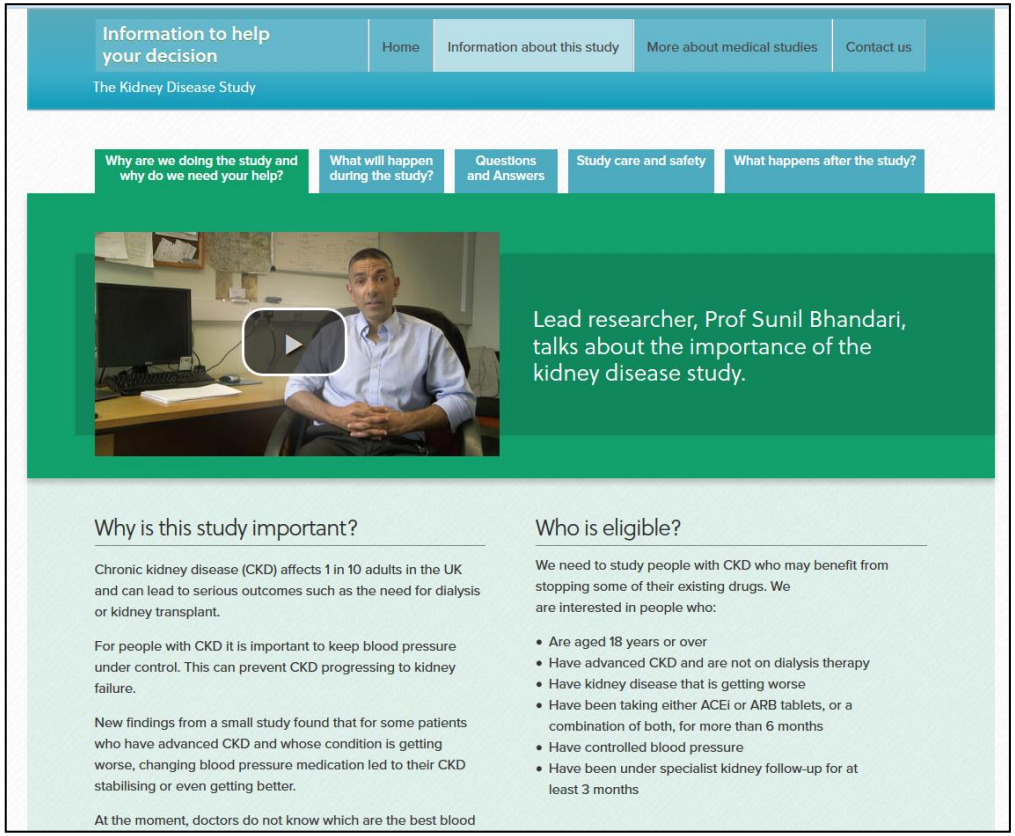
Thank you for reading this information sheet about the STOP-ACEi trial; we would like to invite you to take part. Before you decide whether or not you would like to take part, we would like you to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully and discuss it with others and your doctor if you wish. Do feel free to ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Part 1 tells you the purpose of this trial and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the trial.

To find out more about the study see:

www.stopacei.com



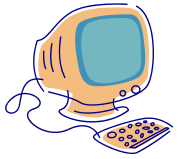
Randomisation

9am – 5pm, Mon-Fri
0800 953 0274

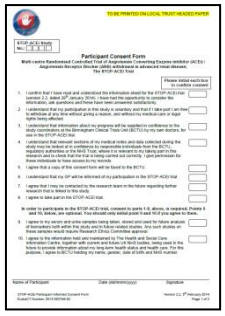
Collect info on
Rand. Notepad

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

Outline

- Year in review
- Patient identification, recruitment and randomisation
- Trial Procedures
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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 procedures – Proposed changes

- Flexible follow-up in line with routine visits for interim assessments
- A more structured path for partial withdrawal
- Removal of patient diaries

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 

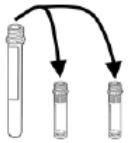
STOP-ACEi ID: __ __ __ __

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

Trial samples

STOP-ACEi Freezer Log

Please update this log every time you put STOP-ACEi samples into the freezer.
You will be asked to submit a copy of the log when you transport samples.
The log should be completed electronically, but you can print a hard copy to keep by the freezer if this helps.

Hospital:	Hull Royal Infirmary	Box number:	099

Box location (freezer and room no.):	Research Freezer, Pathology department, HRI

ID = Participant trial ID number
V = Trial visit. BL = baseline, 12 = 12month, 24 = 24 month, 36 = 36 month
T = Type of sample (i.e. serum, urine or EDTA plasma)

	A	B	C	D	E	F	G	H	I	J
1	ID: 1001 V: BL T: EDTA	ID: 1001 V: BL T: EDTA	ID: 1001 V: BL T: Serum	ID: 1001 V: BL T: Serum	ID: 1001 V: BL T: Serum	ID: 1001 V: BL T: Serum	ID: 1001 V: BL T: Serum	ID: 1001 V: BL T: Urine	ID: 1001 V: BL T: Urine	ID: 1001 V: BL T: Urine
2	ID: 1002 V: BL T: EDTA	ID: 1002 V: BL T: EDTA	ID: 1002 V: BL T: Serum	ID: 1002 V: BL T: Serum	ID: 1002 V: BL T: Serum	ID: 1002 V: BL T: Serum	ID: 1002 V: BL T: Serum	ID: 1002 V: BL T: Urine	ID: 1002 V: BL T: Urine	ID: 1002 V: BL T: Urine
3	ID: 1003 V: BL T: EDTA	ID: 1003 V: BL T: EDTA	ID: 1003 V: BL T: Serum	ID: 1003 V: BL T: Serum	ID: 1003 V: BL T: Serum	ID: 1003 V: BL T: Serum	ID: 1003 V: BL T: Serum	ID: 1003 V: BL T: Urine	ID: 1003 V: BL T: Urine	ID: 1003 V: BL T: Urine
4	ID: 1004 V: BL T: EDTA	ID: 1004 V: BL T: EDTA	ID: 1004 V: BL T: Serum	ID: 1004 V: BL T: Serum	ID: V: T:	ID: V: T:	ID: V: T:	ID: V: T:	ID: V: T:	ID: V: T:
5	ID: 1005 V: BL T: EDTA	ID: 1005 V: BL T: EDTA	ID: 1005 V: BL T: Serum	ID: 1005 V: BL T: Serum	ID: 1005 V: BL T: Serum	ID: 1005 V: BL T: Serum	ID: 1005 V: BL T: Serum	ID: 1005 V: BL T: Urine	ID: 1005 V: BL T: Urine	ID: 1005 V: BL T: Urine
6	ID: V: T:	ID: V: T:	ID: V: T:	ID: V: T:	ID: V: T:	ID: V: T:	ID: V: T:	ID: V: T:	ID: V: T:	ID: V: T:
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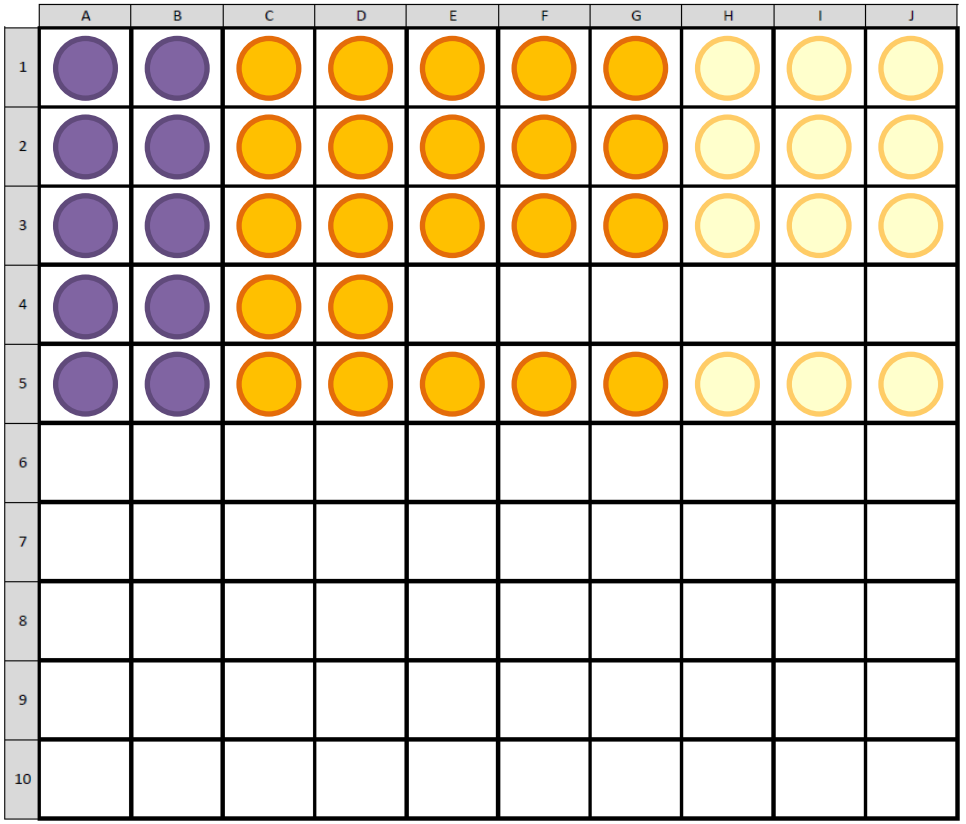


KDQoL-SF™ Questionnaire

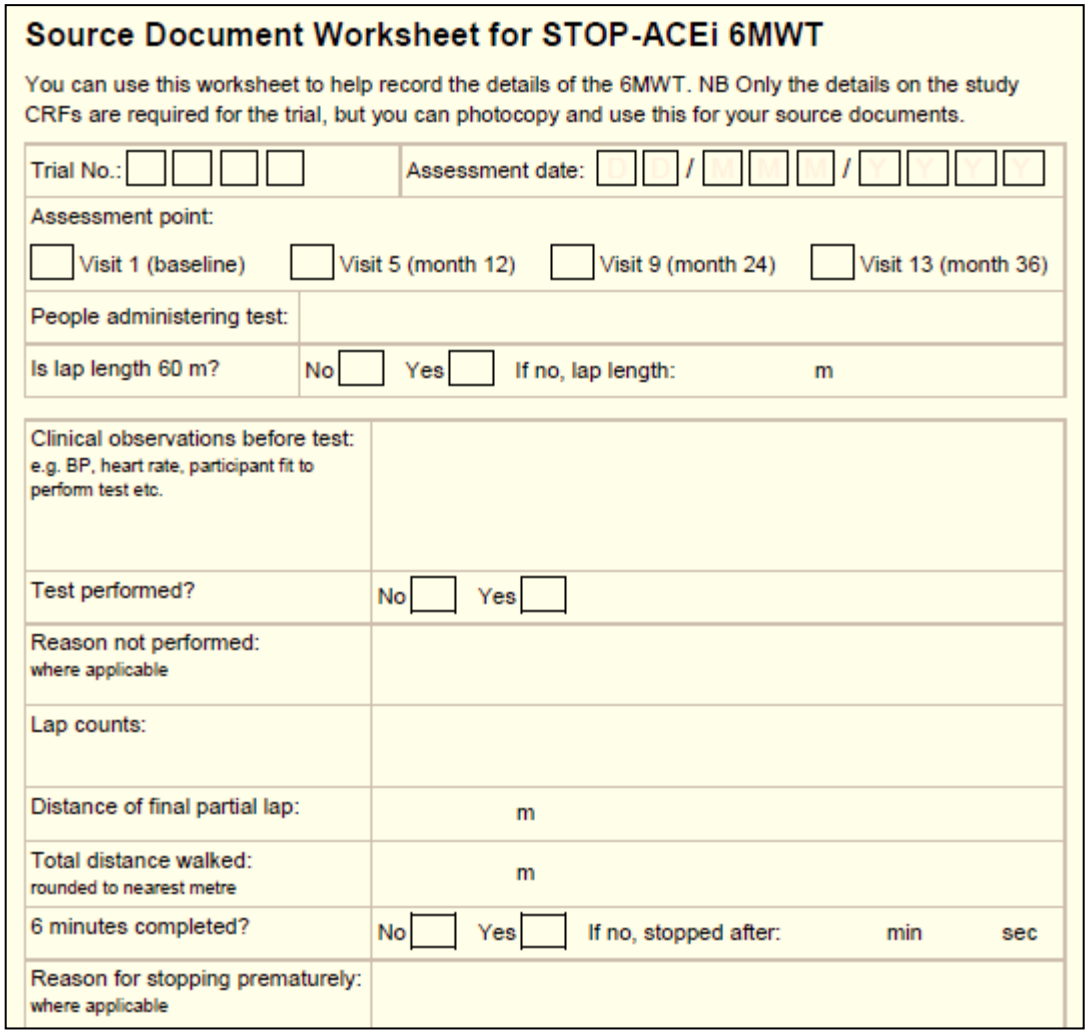
- Importance for the trial
  - Can't assess effect of trial treatment on patient wellbeing without input from the patient
  - Disease-specific
- Completed by participant
- Ideally alone to prevent influence
- RN can check for completeness or causes for concern
- Consider timing – before uncomfortable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

Proposed changes – summary

- Changes to eligibility criteria:
  - Risk of progression demonstrated by proteinuria or by the existing standard of declining renal function
  - Removal of the requirement for 3 months renal follow-up
- Flexible follow-up in line with routine visits for interim assessments
- A more structured path for partial withdrawal
- Improvements to patient information sheets