Statistical Considerations

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

Contents

- Sample Size Considerations
- Primary outcome & analysis
- Secondary outcomes & analyses
- Data Monitoring Committees

Sample Size Considerations

- Sample size is based on the primary outcome
- Primary outcome is renal function at 3 years
  - Measured using the MDRD 4-variable eGFR (Continuous outcome)
- Decide what power (usually 80% or 90%)
  - We have chosen 80% power
- Data for sample size from previous literature
  - Ahmed AK et al. The impact of stopping inhibitors of the renin–angiotensin system in patients with advanced chronic kidney disease
- What MCID we want to detect
  - A MCID of 5 ml/min between the two groups was chosen

Sample Size Considerations

- Limited data was available to calculate sample size
- 1 Observation study provided data on eGFR in patients with advanced CKD

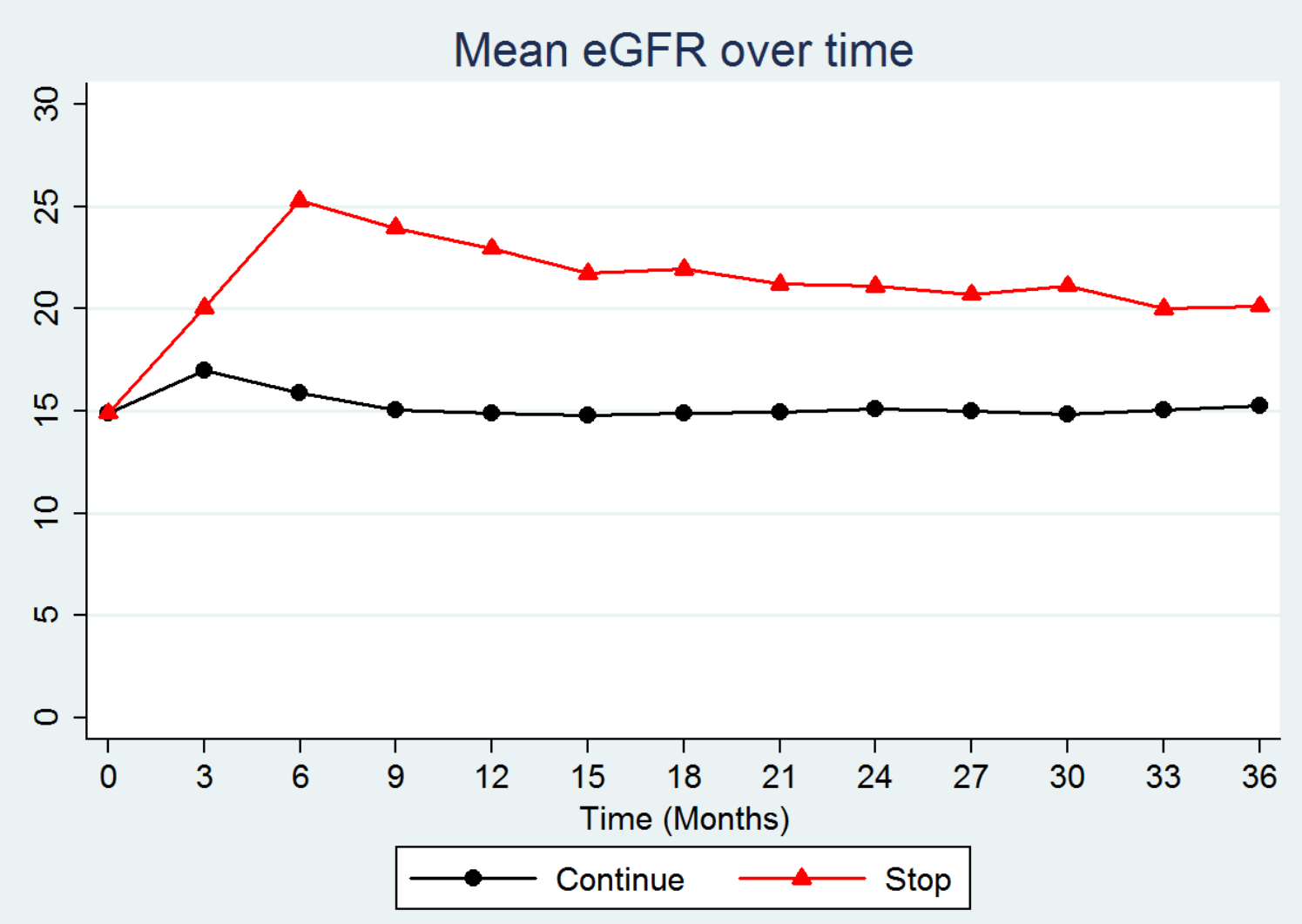
eGFR (ml/min)	12 months before ACEi/ARB stopped	When ACEi/ARB was stopped	12 months after ACEi/ARB was stopped
Mean ± Std.Err [Std.Dev]	22.9 ± 1.4 [10.1]	16.38 ± 1 [7.2]	26.6 ± 2.2 **[15.9]**

- The largest standard deviation (15.9) was chosen to estimate variability for eGFR
- A MCID of 5 ml/min between the two groups was chosen
- With 80% power, alpha=0.05 and allowing for 20% attrition gives a total sample size of 410 participants (205 per arm)
- Sample size based on a 2-sample T-Test
- Sample size assumptions to be monitored by DMEC

Primary Outcome analysis

- The primary outcome is the continuous measure eGFR at 3 years
- Primary analysis will be using an ANCOVA model adjusting for baseline eGFR score, all minimisation variables and any other covariates deemed important to do so
- Data for eGFR are collected every 3 months for all patients in the standard follow-up clinic
- Hence as a secondary analysis a repeated measures analysis, including treatment by time cross-term will be carried out across the entire 3 years of follow-up
- Results will be presented as mean difference in eGFR with 95% CI
- Longitudinal plots of mean changes from baseline over time by treatment group for visual inspection

Primary Outcome analysis



Secondary Outcomes

Continuous Outcomes

- Blood pressure between groups
- Cystatin-C levels between groups
- Participant physical function (measured using the 6-minute walk test)
- Urine protein excretion between group
- Haemoglobin concentration between groups
- ESA dose between groups

Time to event outcomes

- Time taken to reach ESRD or need for renal replacement therapy

Quality of life (QOL) outcomes

- Participant QOL and wellbeing (measured using KDQOL-SF v.1.3 questionnaire)

Secondary Outcomes

Safety data & Categorical outcomes

- Hospitalisation rates from any cause
- Cardiovascular events
  - heart failure, hypertension, myocardial infarction, stroke
- Adverse events
- Mortality rates
- N of participants starting renal replacement therapy or sustaining a >50% decline in eGFR

Secondary Outcomes analyses

- **Continuous Endpoints**
  - Analysed in the same manner as the primary endpoint
- **Categorical (Dichotomous endpoints)**
  - Proportions and percentages will be compared between arms using Chi-squared test
  - Relative risks and 95% CI's will be calculated
  - Logistic regression may be used to adjust for any covariates
- **Time to event data**
  - Kaplan-Meier survival curves will be constructed for visual presentation of time-to-event comparisons
  - Log-rank test and Cox proportional hazard model will be used
  - Treatment effects will be expressed as hazard ratios with 95% CI's

Subgroup analyses

- Several a priori subgroup analyses are planned:
  - Diabetes
    - Type 1 diabetes, Type 2 diabetes (including insulin-treated Type 2 diabetes), Non-diabetic
  - BP as mean arterial pressure (<100, ≥100)
  - Age (<65 years, ≥65 years)
  - Proteinuria (PCR<100, ≥100)
  - eGFR (<15 ml/min, ≥15 ml/min)
- These analyses will be treated as hypothesis-generating
- Subgroup analysis will employ a test of interaction
- All analyses will be conducted using intention to treat (i.e. analysing in the group to which the subject was randomised)
- Full statistical analysis plan to describe all analysis in detail

Data Monitoring Committee

- It comprises of 3 people:
  - Dr John Firth (Chair) – Consultant Nephrologist
  - Dr Paul Kalra – Cardiologist
  - Mrs Merryn Voysey – Independent Statistician

- Their role will be to review:
  - study progress (i.e. recruitment rates, form return rates, baseline data)
  - sample size assumptions
  - outcome efficacy
  - mainly all of the safety data

- DMC will meet annually but can meet more regularly (i.e. every 4-6 months) if the DMC wishes to

Data Monitoring Committee

- DMC make recommendations to the Trial Steering Committee

- Possible recommendations include:
  - No action needed, trial continues as planned
  - Early stopping due, for example, to clear benefit or harm of treatment, futility, or external evidence

- Any recommendations on stopping the trial early will be based on a balance between safety, efficacy and any external evidence

- A DMEC charter outlining the terms of reference (including information on stopping rules) is agreed with the DMEC