Supplementary Online Content 5


Statistical Analysis Plan
Protocol Number: GI-R-01-2011

Statistical Analysis Plan
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1 Introduction

1.1 Study synopsis

The TESTING (Therapeutic Evaluation of STeroids in IgA Nephropathy Global) study is a multicenter, double-blinded, randomized placebo-controlled trial designed to evaluate the long-term efficacy and safety of oral methylprednisolone, on a background of maximal tolerated dose of renin angiotensin system (RAS) inhibitor therapy, in preventing kidney events in patients with IgA nephropathy with features suggestive of a high risk of disease progression.

In brief, after a 4 to 12 week run-in phase to ensure participants are receiving standard guideline based care (blood pressure control and the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) at the maximum tolerated/labelled dose), eligible patients will be randomised to methylprednisolone or matching placebo. All participants will continue to receive standard care throughout the trial.

1.2 Objectives

Protocol Primary objective

To determine if adding oral methylprednisolone to best available standard care for 6-8 months reduces the risk of the composite outcome of persistent 40% reduction in eGFR, end stage kidney disease and death due to kidney disease, compared to matching placebo, in patients with progressive IgA nephropathy.

Protocol Secondary objectives

To determine if adding oral methylprednisolone to optimal background care, compared to placebo:

1. Reduces the risk of the composite outcome comprising ESKD, persistent 40% reduction in eGFR and death due to any cause.
2. Reduces the risk of the composite outcome comprising ESKD, persistent 50% reduction in eGFR and death due to any cause.
3. Reduces the risk of each of ESKD and renal death
4. Affect safety outcomes with special focus on:
   • Serious infections requiring hospitalisation
   • New onset diabetes mellitus
   • Clinically apparent gastrointestinal haemorrhage requiring hospitalisation
   • Clinically evident fracture or osteonecrosis
   • Cardiovascular events, defined as a composite of myocardial infarction, stroke, heart failure requiring hospitalisation or death due to cardiovascular disease.
2 Study Population

2.1 Target population
The target population will consist of patients with primary IgA nephropathy who are at high risk of progression to kidney failure. The strongest clinical determinants of the risk of kidney failure are renal function, proteinuria, and hypertension.

2.2 Inclusion Criteria
1) IgA nephropathy, proven on renal biopsy.
2) Proteinuria (on most recent test): ≥1.0g/day while receiving maximum tolerated dose of RAS blockade
   - ≥1.0g/day on most recent available lab tests on Visit 1
   - ≥1.0g/day while receiving maximum tolerated dose of RAS blockade on Visit 3
3) eGFR (on most recent test): 20 to 120ml/min per 1.73m$^2$ (inclusive)
   - Serum creatinine and Proteinuria evaluation for eligibility will be determined on at least two visits during run-in phase.
   - Estimated GFR will be calculated using the equation of CKD-EPI (Appendix A)
   - Patients with eGFR >120 ml/min per 1.73m$^2$ at screening stage while reaching less than 120 ml/min per 1.73m$^2$ after tolerated RAS inhibition therapy at visit 3 are eligible for this study

2.3 Exclusion Criteria
Patients who meet any of the following exclusion criteria will not be included in the trial

1) Indication for immunosuppressive therapy with corticosteroids, such as:
   a. Minimal change renal disease with IgA deposits
   b. Crescents present in >50% of glomeruli on a renal biopsy within the last 12 months.
2) Contraindication to immunosuppressive therapy with corticosteroids, including
   a. Active infection, including HBV infection (HBsAg-positive or HBeAg-positive, or serum detectable HBV-DNA) or clinical evidence of latent or active tuberculosis (nODULES, cavities, Tuberculoma, etc.)
   b. Malignancy within the last 5 years, excluding treated non-melanoma skin cancers (i.e. squamous or basal cell carcinoma)
c. Current or planned pregnancy or breastfeeding  
d. Women of childbearing age who are not able or willing to use adequate contraception (See Appendix 5)

3) Systemic immunosuppressive therapy in the previous 1 year.
4) Malignant /uncontrolled hypertension (＞160mm systolic or 110mmHg diastolic).
5) Current unstable kidney function for other reasons, e.g. macrohaematuria induced acute kidney injury (past episodes are not a reason for exclusion)
6) Age <14 years old
7) Secondary IgA nephropathy: e.g. due to lupus, liver cirrhosis, Henoch-Schonlein purpura
8) Patients who are unlikely to comply with the study protocol in the view of the treating physician
9) Participation in another trial (current or within the last month)

3 Study Design

3.1 Aim & Hypothesis
This is a double blind, randomised, parallel-group, two-arm, long-term study that comprises 3 study phases i.e. Run-in phase, Treatment phase and Follow-up phase. This study aims to evaluate the long-term efficacy and safety of a 6-8 month regimen of tapering corticosteroid therapy i.e. oral methylprednisolone on a background of routine Renin Angiotensin System (RAS) inhibitor therapy in patients with IgA nephropathy and features suggesting a high risk of renal progression.

3.2 Study design and study drug dosing regimen
Patients with IgA nephropathy who are at high risk of progression to kidney failure are randomised in a 1:1 ratio to either methylprednisolone or matching placebo in a double-blind fashion.

After a 4-12 week run-in phase for background therapies optimization, participants randomised to the intervention group will receive oral methylprednisolone 0.6-0.8mg/kg/d (up to a maximum of 48 mg/day) for 2 months. The dose is then tapered by 8mg every month until the course is completed. Investigators will have the option of reducing the treatment dose from 8mg to 4mg for one month prior to cessation. Individuals randomised to the placebo group will follow an identical protocol using matching placebo tablets. The total treatment duration will therefore be 6-8 months for all participants. Patients were to be evaluated once every 1-3 months during methylprednisolone therapy as usual practice. The third phase is post-treatment follow up.
### 3.3 Expected duration of trial

The total duration of this study was expected to be at least 6 years with recruitment of at least 2 years and a subsequent follow-up of at least 4 years. All randomised subjects were expected to participate in the active treatment phase of up to 8 months duration and be followed up for at least 4 years post-treatment until the earliest of any of the following:

- Completion of the follow-up period (final visit)
- Death or ESKD
- Withdrawal of consent, by the subject or legal surrogate, or withdrawal by the investigator due reasons mentioned above
- Premature study termination as defined by study protocol Version 5 of 13 May 2015

### 3.4 Power Calculations

A sample size of 750 patients will provide more than 90% power (α=0.05) to detect a 30% risk reduction with a steroid based treatment approach after an average follow-up of 5 years, equating to a 33% actual effect incorporating a 10% treatment drop out. The study has 80% power to detect a 26% RRR, equating to a 28% RRR due to the treatment after accounting for 10% treatment dropout.

The sample size calculations were performed using the log-rank test and assume an annual combined rate of 40% decline in eGFR or ESKD of 12% in the placebo arm. The study was designed to continue until at least 335 primary endpoints had been observed.

### 3.5 Premature termination of the study

The study protocol specifies that the study could be closed at any time at the request of the study steering committee, the Investigator, or a regulatory authority, with proper and timely notification of all parties concerned. The Independent Ethics Committee will be informed and the Coordinating Centre or the investigator will supply reason(s) for the termination or suspension, as specified by the applicable regulatory requirements.

### 3.6 Outcome

#### 3.6.1 Primary outcome

The primary, protocol-specified outcome is progressive kidney failure which is a composite of a persistent 40% decline in estimated glomerular filtration rate (eGFR), the development of end stage kidney disease (ESKD) as defined as a need for maintenance dialysis or kidney transplantation, and death due to kidney disease.

1) **Persistent ≥ 40% reduction in eGFR**
The baseline eGFR is defined as the mean of the two eGFRs from Visit 3 (pre-randomisation visit) and Visit 4 (randomization visit), calculated by CKD-EPI formula (appendix A) from serum creatinine (mg/dl).

The follow-up eGFR values will be compared to the baseline eGFR to determine whether a 40% reduction relative to the baseline eGFR has occurred. A “persistent” ≥ 40% eGFR reduction is established by the occurrence of 2 consecutive follow-up eGFR values which are at least 40% smaller than the baseline GFR, where the second value is obtained no less than 4 weeks after the initial decline or until the final available study visit.

2) End stage kidney disease

ESKD is defined as the receipt of kidney transplantation, initiation of dialysis, the satisfaction of certain criteria where dialysis is unavailable or been refused by the patient as described further below, or renal death where criteria for ESKD has not previously been met. ESKD will be diagnosed if dialysis is performed for 30 days or more that is known not to recover.

When dialysis is not readily available in some parts of the world or the patient refused dialysis, the diagnosis of ESKD will be the presence of either symptomatic or advanced asymptomatic uremia defined using the following criteria:

(i) eGFR <15 mL/min/1.73 m² on 2 blood tests at least 30 days apart AND the presence of symptoms ascribed to uraemia

(ii) eGFR <8 mL/min/1.73 m² on two blood tests at least 30 days apart which may be with or without the presence of symptoms ascribed to uraemia

3) Renal death:

Patients with eGFR<15ml/min/1.73m² may die prior to initiating renal replacement therapy.

Such events will be classified as renal death when they satisfy the following 3 criteria

1. The patient with eGFR<15ml/min/1.73m² dies AND

2. The patient has refused RRT or dialysis is not available AND

3. The death cannot be attributed to a specific aetiology (e.g. CV death, Stroke, progression of cancer, violence)

The diagnosis of renal death is not intended for subjects in whom dialysis is not offered or withdrawn because of advanced cancer, severe sepsis, advanced heart failure, or terminal organ failure. In such instances, the primary diagnosis that led to withholding RRT will be designated the cause of death.

3.6.2 Protocol-specified secondary outcomes

The protocol-specified secondary outcomes, which build on the protocol’s objectives, are:
1. The composite of outcome of ESKD, persistent 40% decrease in eGFR and death due to any cause.
2. The composite outcome comprising ESKD, persistent 50% reduction in eGFR and death due to any cause.
3. The composite of outcome of ESKD and renal death
4. The individual components of the composite, i.e. persistent 40% decrease in eGFR, persistent 50% decrease in eGFR, ESKD, renal death and all cause death
5. Change in eGFR, considered using the following:
   • Rate of eGFR decline (ml/min/1.73m² per year)
     - Defined for each individual patient using the slope from least squares linear regression of all eGFR estimates over time
   • Rate of eGFR decline (ml/min/1.73m² per year) defined as above, but excluding the treatment period with highest steroid exposure (i.e. excluding eGFR values from month 1 (visit 5) and month 3 (visit 6).
   • Trajectory of eGFR over time using all available eGFR estimates, as outlined in section 5.2.1
6. Time average proteinuria, calculated as follows:
   • For each patient, the proteinuria measurements will be from visits V4, V6, V7, V9, V13, and then yearly thereafter during follow-up
   • Time average proteinuria for each patient will be the mean of \((3*V4 + 3*V6 + 6*V7)/12\), V9, V13, and each yearly measurement thereafter
7. Safety outcomes including:
   • All serious adverse events
     Definition: SAEs are reported by investigators using the following guidance: SAEs are defined as any untoward medical occurrence that meets one of more of the following criteria:
     • Results in death
     • Is life-threatening
     • Requires inpatient hospitalisation or prolongation of existing hospitalisation
     • Results in persistent or significant disability/incapacity
     • Is a congenital anomaly/birth defect
     • Serious infections requiring hospitalization
     • New onset diabetes mellitus
     • Clinically apparent gastrointestinal haemorrhage requiring hospitalization.
• Clinically evident fracture or osteonecrosis
• Pregnancy
• Cardiovascular events, defined as a composite of myocardial infarction, stroke, heart failure requiring hospitalization or death due to cardiovascular disease.

3.6.3 Exploratory secondary outcomes
1. The composite outcome comprising ESKD, persistent 25% reduction in eGFR and death from any cause.
   Definition of persistent 25% reduction in eGFR: a reduction to less than 25% of baseline eGFR that stays below this level on all subsequent eGFR measurements during follow-up
2. Individual component of persistent 25% decreased in eGFR
3. Proportion of patients in complete proteinuria remission (definition as 3.6.2 #6) AND stable renal function (eGFR loss of < 5 ml/min/1.73m² from baseline eGFR) evaluated at the following time points: 6, 12 and 24 months, and at the end of follow-up
4. Mean annual change of 1/creatinine concentration
   Defined for each individual patient using the slope from least squares linear regression of all reciprocal of serum creatinine values over time
5. Disappearance microhaematuria –
   Defined as urine analysis of RBC < 5phf at the end of the study/last available visit for those participants with micro or macrohaematuria at randomization visit.
6. Change in proteinuria, considered using the following:
   • Trajectory of proteinuria over time using all available proteinuria estimates, as outlined in section 5.2.3 #6
   • Achieving complete proteinuria remission (CR), partial proteinuria remission (PR) and total proteinuria remission (TR) (i.e. complete and partial remission combined), defined as follows:
     Complete proteinuria remission (CR) is defined as 24 hour urinary protein <200mg/day.
     Partial proteinuria remission (PR) is defined as proteinuria less than 50% of baseline by 24 hour urinary protein, AND <1gm/day.
   • Achieving proteinuria remission will be considered as follows (see section 5.2.3 #6 for more details)
     a) Time to achieving persistent CR, PR and total remission, with “persistent” defined as maintaining the CR or PR definition on all subsequent measurements of proteinuria until the end of follow-up
     b) Proportion of patients in proteinuria remission (CR, PR and TR) evaluated at the following time points: 6, 12 and 24 months, and at the end of follow-up. This considers only the proteinuria status at each given time point.
4. Analysis principles

4.1 General principles
Comparison will be made for all of the outcomes by comparing all those allocated to methylprednisolone versus all those allocated to the control arm on an intention to treat (ITT) basis. All randomized participants will be analysed in the group to which they were assigned regardless of protocol violations. Cox proportional hazards analysis and Kaplan-Meier plots will be used to compare time to events among the two groups. No adjustment will be made for multiple testing across the primary endpoints. However the outcomes are clearly categorized by degree of importance (primary, main secondary and exploratory secondary) and a limited number of subgroup analyses are pre-specified. All missing information will be treated as missing data without imputation. All statistical tests will be two-tailed and a 5% significance level maintained throughout the analyses. In case of borderline statistical significance for the primary endpoint (i.e. a p-value between 1.66% and 5%), results will be interpreted with caution. Heterogeneity across subgroups will be tested by adding an interaction term to the appropriate statistical model. Summaries of continuous variables which are normally distributed will be presented as means and standard deviations or medians and inter-quartiles for skewed data, while categorical variables will be presented as frequencies and percentages.

4.2. Blinding
The current statistical analysis plan has been developed by a group nominated by the TESTING Steering Committee which includes statisticians and clinical researchers with nephrology expertise. The group will not be unblinded until after the SAP has been fully signed off. The statistician(s) responsible for interim monitoring and liaising with the DSMB will not provide input to the SAP. The results will be unblinded to the rest of the team once the final statistical report has been completed.

4.3 Patient deposition
Flow of patients through the study will be displayed in a “CONSORT” diagram as in the appendix B. Numbers of patients who were registered, fulfilled eligibility criterion, together with reasons for exclusion, and number randomised by study centre will be summarised.

4.4. Patient follow up
A separate figure (Appendix C) will summarise the follow up method for randomized patients indicating the numbers of patients who withdrew consent (with follow up) and those true loss to follow up.

4.5 Characteristics of patients and baseline comparisons
Description of the following baseline characteristics will be presented by treatment group. Discrete variables will be summarized by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator (which will be less than the number of patients assigned to
the treatment group) will be stated in either the body or a footnote in the corresponding summary table. In some instances, additional frequencies and percentage of patients in each category will be reported as indicated in the list below. Continuous variables will be summarized by use of standard measures of central tendency and dispersion using mean and standard deviation and/or quantile points at 0.25, 0.5 and 0.75 where appropriate. Free text entries for fields collecting both categorical and free text information (e.g. ethnicity) will be assessed and assigned to a category if appropriate at the discretion of the Study Director.

- Age
- Sex
- Ethnicity
  - Caucasian
  - Chinese
  - South-East Asian
- Smoking status
- Macrohaematuria
- History of hypertension
- History of tonsillectomy
- Previous systemic exposure to corticosteroid.
- Previous exposure to other immunosuppressant therapy
- Family history of IgA nephropathy
- Co-morbidity :
  - Diabetes Mellitus
  - Coronary heart disease
  - Stroke
  - Heart failure
  - Peptic ulcer
- Medication
  - ACE/ARB
  - Proportion achieved maximum labelled dose of ACE/ ARB
  - Concomitant medications

### 4.6 Physical characteristics

- Height, weight, BMI (derived from height and ideal body weight)
- Blood pressure: systolic and diastolic blood pressure
- Heart rate.

### 4.7 Kidney biopsy parameter based on Oxford Classification for IgA nephropathy

- Mesangial hypercellularity
- Segmental glomerulosclerosis
- Endocapillary hypercellularity
- Tubular atrophy/ interstitial fibrosis
- Percentage of glomeruli with crescents in the kidney biopsy

### 4.8 Laboratory Results

Continuous variables will be summarized by use of standard measures of central tendency and dispersion using mean and standard deviation as well as quartile points at 0.25, 0.5 and 0.75 where appropriate stratified by measurement time points (screening, randomization, 3, 6, 12 and 24 months) and by treatment group. To assess the treatment effect on laboratory
variables, a linear mixed effects model with a random intercept, with treatment and time (categorical) as fixed effects will be used. Whenever appropriate, a fully unstructured covariance model will be used at indicated time points at baseline, 3, 6, 12 and 24 months of follow-up.

4.8.1 Laboratory measures

- Haemoglobin
- Total white blood cell count
- Platelet count
- Lymphocytes
- Sodium
- Potassium
- Chloride
- Fasting blood sugar
- Reported Calcium
- Phosphate
- Uric acid
- Bicarbonate
- Urea
- Creatinine
- eGFR (CKD-Epi)
- Total protein
- Albumin
- Total bilirubin
- Alanine aminotransferase
- Alkaline phosphatase
- C-reactive protein
- Parathyroid Hormone
- Total cholesterol

4.8.2 Urinary Measures

- Urinary analysis
  - Red blood cell per HPF
  - White blood cells per HPF
- 24 hours urine protein* (g/24-hour)
- 24 hours urine creatinine§ (mmol/24-hour)

*Twenty-four hour urinary collections are considered incomplete if collections had a measured volume of less than 500mL or greater than 6000mL, or an outlying 24-hour creatinine excretion§ (less than 4mmol/day or greater than 25mmol/day in women and less than 6mmol/day or greater than 30mmol/day in men). The values will be considered missing.

5. Specific Analysis Methods

5.1 Primary outcomes
Survival curves and estimated median survival times will be generated according to the Kaplan-Meier method, and compared using the log-rank test. Cox proportional hazards analysis will be performed to generate a hazard ratio between the two groups. The primary outcome is time from randomization to the first instance of a 40% decline in eGFR, ESKD or death due to renal disease, censored at the date when patients died (for causes other than
renal disease), were lost to follow up, withdrew from study, or at the end of study visit, whichever occurred first.

**Sensitivity analysis:**
A sensitivity analysis will be done including or excluding patients who reached the primary endpoint but the endpoint is not confirmed yet (e.g. Patient commenced on dialysis but has not reached 30 days of confirmation, at the time of analysis)

**Sub-group analysis:**
The following protocol-specified subgroups will be performed for the primary endpoint for stratified analysis:
1. Degree of proteinuria (<3.0g/day, ≥3.0g/day) at baseline
2. eGFR <50 versus ≥50ml/min per 1.73m²) at baseline
3. Histological lesion scoring (E1 or E0)

The following additional subgroup analysis will also be performed for the primary endpoint:
4. Baseline maximum tolerated dose of ACE or ARB (>80%, 50-79% and <50% achieved of maximum labelled dose)

Heterogeneity across subgroups will be tested by adding an interaction term to the appropriate statistical model.

**5.2 Secondary outcomes**
Time to secondary outcome events will be analysed similarly to the primary outcome analysis.

**5.2.1 Change in eGFR:**
The rate of eGFR decline (ml/min/1.73m² per year) for each patient will be acquired from the slope of a linear regression model (If the pattern of decline appears near linear) of all eGFR over time, the mean rate of eGFR decline will compared between the two treatment groups using a t-test. A sensitivity analysis will be performed using the same methodology, but excluding eGFR values at the time of high-dose treatment exposure (i.e. excluding values from month 1 and month 3, or visits 5 and 6 respectively).

The trajectory of eGFR over time will be presented by graphing the mean value of eGFR for the two randomized groups (instead of individual patients) at each time point (i.e. randomization, 3, 6, 12 and 24 months), and will be modelled using mixed models (with visual inspection to confirm an assumption of linearity) The difference of average eGFR over time will be shown in the graph using linear mixed model with assumption of exchangeable correlation among visits. Autoregressive structure will be used in the mixed model as sensitivity analysis.

The trajectory of eGFR over time will be visually presented by plotting the mean eGFR at each time point in the different treatment groups, and will be modelled using mixed models with time and treatment groups as fixed effects. Random effects will be assumed to be normally distributed and independent of each other. The model will assume a linear rate of
GFR decline within each patient, this will be confirmed using the visual plot and alternative modelling strategies accounting for non-linear functional forms will be adopted if needed.

5.2.2 Time average proteinuria:

The distribution of proteinuria will be examined and whenever appropriate a log transformation may be applied. The mean time average proteinuria for each treatment group will be compared using a t-test.

5.3 Exploration secondary outcomes

1. The composite outcome comprising ESKD, persistent 25% reduction in eGFR and death from any cause.

2. Individual component of persistent 25% decreased in eGFR

1 & 2. Will be analyzed as described in 5.2.

3. Proportion of patients in complete proteinuria remission (definition as 3.6.3 #6) AND stable renal function (eGFR loss of < 5 ml/min/1.73m² from baseline eGFR) evaluated at the following time points: 6, 12 and 24 months, and at the end of follow-up

Due to differential follow-up times, the number of patients evaluated at each time point will be clearly indicated

4. Mean annual change of 1/creatinine concentration

Defined by the mean slopes resulting from regression of time to the reciprocal of the serum creatinine concentration at baseline, 6, 12 and 24 months.

The relation between time and 1/Creatinine concentration will be individually described by a linear regression line using method described above for rate of eGFR decline. In case of more than two missing observations per individual a slope of 0 (e.g. no annual change) will be assumed.

5. Disappearance of microhaematuria

A logistic regression model will be fitted to the data of the rates involving treatment. In the case of a missing observation at the final study visit, this will be handled as a treatment failure.

6. The change in proteinuria

The time to persistent proteinuria remission will be analysed using CR and PR as separate outcomes, and a composite of total remission (CR or PR), censored at the end of follow-up. Cox proportional hazards models will be used to generate a HR to compare the two groups. When analysing time to proteinuria remission, the outcome will consider persistent proteinuria remission as defined in 3.6.3 #6.

The proportion of patients achieving CR, PR and TR at the following fixed time points will be evaluated and compared across the treatment groups: 6, 12, and 24 months, and at the end of follow-up. The number of patients evaluated at each time point will be clearly indicated. When analysing proteinuria remission (with definitions in 3.6.3 #6) at specific time points,
the outcome will consider the proteinuria remission status only at the appropriate time point

5.4 SAE outcomes

SAE event rates will be compared as 3.6.2 point #7. Summary of each safety endpoints will be provided. Continuous outcome will be summarised by their mean (SD) or median (IQR) as appropriate, while binary outcome will be summarised by n and percentages. In addition a listing of SAEs will be presented according to randomisation group, which will include the time from randomization, the current treatment dose, and cumulative dose of study drug at the time of the SAE.

Survival outcome will be summarised by proportion of events by group and their median times will be reported. The intervention effect on each SAE will be assessed in relation to the study drug based on cumulative dose and/or dose exposed at the time of SAE occurrence, and the time from randomization to the SAE occurrence.

Further analyses: Further analyses for the cohort phase of the study will be subject to a separate report when data are available.

Appendices

Appendix A. CKD-EPI formula

\[
GFR = 141 \times \min \left( \frac{S_{cr}}{\kappa}, 1 \right)^{\alpha} \times \max \left( \frac{S_{cr}}{\kappa}, 1 \right)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \times [\text{if female}] \times 1.159 \ [\text{if black}]
\]

where:

- \(S_{cr}\) is serum creatinine in mg/dL,
- \(\kappa\) is 0.7 for females and 0.9 for males,
- \(\alpha\) is -0.329 for females and -0.411 for males,
- \(\min\) indicates the minimum of \(S_{cr}/\kappa\) or 1, and
- \(\max\) indicates the maximum of \(S_{cr}/\kappa\) or 1.
Appendix B. Patient deposition
(Sample to be redrawn: Patient deposition (Enrolment, randomization and follow up)
Appendix C. Method of follow-up for randomized patients

Appendix D. Sample figures and tables.
See separate attachment.