# EMPA-KIDNEY: effects of empagliflozin on healthcare resources and quality of life

## Health economics analysis plan

## 1. Introduction

This document provides a Health Economics Analysis Plan (HEAP) for the analyses of healthcare resources (hospital admissions, medications, treatments of end stage kidney disease (ESKD)), progression to chronic kidney disease (CKD) stages, health-related quality of life (QoL) and quality-adjusted life years (QALYs) in the EMPA-KIDNEY trial[1].

The analytical approaches, wherever possible, follow those set out in the EMPA-KIDNEY trial's data analysis plan (DAP) v.1.2[2].

## 2. Aims

1. To assess effects of allocation to empagliflozin on hospital admissions, progression to advanced CKD (stages 4, 5 and ESKD), healthcare resource use and cost, and generic health-related quality of life (QoL)
2. To report cost-consequences analysis of effects of allocation to empagliflozin on differences in healthcare resources, costs and outcomes between treatment arms

## 3. Definitions of estimands and outcomes

### *3.1. Estimands*

The estimands of interest for aim 1 will be:

- For all cause hospital admissions (overall and by MedDRA System Organ Class (SOC)): hazard ratio of allocation to empagliflozin for all occurrences during trial follow-up.
- For progression to more advanced CKD: hazard ratio of allocation to empagliflozin for the first occurrence of progression:
    - ESKD (requiring dialysis or kidney transplant) for all the participants
    - CKD stage 5 or ESKD whichever earlier for participants with baseline eGFR > 15 ml/min/1.73 $m^2$
    - CKD 4, CKD 5 or ESKD whichever earlier for participants with baseline eGFR > 30 ml/min/1.73 $m^2$
- For healthcare resource use: rate of resource use or costs between treatment arms during trial follow-up with outcomes defined as:
    - Days in hospital and costs of hospital admissions (overall and by MedDRA SOC category)
    - Days on and costs of concomitant medication by category of interest
    - Costs of ESKD (overall and by dialysis / kidney transplant)
- For QoL, measured using EQ-5D utility: the difference in the annual rate of change in QoL across follow-up time between the group allocated empagliflozin and the group allocated placebo

All the comparisons will be performed in the target population for participants allocated empagliflozin relative to those allocated placebo, conditional on the baseline covariates specified in the minimized randomization algorithm (see section h)).

The estimand of interest for aim 2 will be:

- For active treatments use: mean over trial follow-up
    - Days on empagliflozin and costs of empagliflozin
- For healthcare resource use: difference in means between treatment arms over trial follow-up
    - Days in hospital and costs of hospital admissions (overall and by MedDRA SOC category)
    - Days on and costs of concomitant medications (overall and by category)
    - Costs of ESKD (overall and by dialysis type / kidney transplant)
- For quality-adjusted life year (QALY): difference in mean QALYs over trial follow-up between treatment arms

All the comparisons will be performed for participants allocated empagliflozin relative to those allocated placebo (see section h)).

### *3.2. Outcome assessment*

#### *3.2.1. Hospital admissions, days in hospital and costs of hospital admissions*

Outcomes related to hospital admissions, overall and by MedDRA SOC, include:

- time to occurrences of hospital admission (all first and recurrent admissions)
- days in hospital
- costs of hospital admissions

When patients experienced an adverse event (AE), whether this AE led to a hospital admission would be recorded. Each AE leading to a hospital admission was assigned a MedDRA SOC code in the trial CRF. We will analyse hospital admissions overall and by SOC.

The start date of the hospital admission would be the start date of the AE leading to the admission; the discharge date of the admission would be derived based on the start date of the admission and the duration of hospital admission (recorded in trial case report form (CRF)). In the case of missing information for the duration of the hospital admission, the end date of the AE leading to the hospital admission would be assumed the discharge date for the admission.

Some patients experience multiple AEs leading to several overlapping hospital episodes (e.g. patient concurrently treated by different consultants in hospital). In the analysis, the overlapping inpatient episodes will be grouped into one hospital admission. The start date and the discharge date of the admission will be the start date of the first inpatient episode and the discharge date of the last inpatient episode respectively. For the analyses by SOC, in the case of overlapping episodes within the same SOC the same approach will be followed by grouping these episodes into one admission. It is noted that the sum of days in hospital across SOCs is likely to exceed the overall number of days in hospital due to the overlapping admissions; this will be acknowledged when reporting results by SOC.

*Time to occurrences of hospital admission*

The time to occurrence of each hospital admission will be generated by taking the number of days from randomisation to the first day of the relevant hospital admission. Strictly speaking, a participant would not be considered at risk of another hospital admission until the end of the

admission, but due to the complexity of programming in these types of models, we will instead assume that each participant would be at risk of another hospital admission on the following day of the same admission.

*Days in hospital*

Days in hospital will be derived from durations of hospital admissions based on the start and discharge date of the admissions. Admission with discharge on the same date would be assigned one day in hospital.

*Costs of hospital admission*

Following grouping of overlapping episodes, each hospital admission will be mapped into Healthcare Resource Group (HRG) and costed using respective HRG unit costs from the National Schedule of Reference Costs. HRGs are groups of hospital admissions with similar hospital resource use, used for hospital care reimbursement in the UK. We will use the NHS (England) Reference Costs HRG4+ 2022/23 National Costs Grouper software[3] to map the hospital admissions into HRGs, and cost the HRG with the National schedule of reference costs 2021/2022[4], the most recent versions of the grouper and reference costs.

As the HRG grouper requires the diagnosis codes (ICD-10) and/or procedure codes (UK OPCS classification of interventions and procedures version 4, OPCS-4) for mapping hospital admissions into HRGs, we will convert the MedDRA preferred term codes (lowest MedDRA code level used in the trial) into ICD-10 and/or OPCS-4 codes prior to mapping hospital admissions into HRGs.

Each hospital admission, once mapped into HRGs, has at least one core HRG, and may have several further unbundled HRGs that attract additional costs. The core HRGs within typical duration and unbundled HRGs will be costed based on the unit cost for the HRG from the reference costs. However, the unit cost for a HRG in NHS differs depending on the type of admission: elective, non-elective short stay (<2 days), non-elective long stay (≥2 days), day case, and regular day or night admission. We will use the weighted unit costs using the number of admissions for all types of admission at HRG level as reported for the NHS in England in year 2021/2022[4]. The final cost of the hospital admission will be the cost of core HRG and any unbundled HRGs.

For hospitalizations not successfully mapped into HRGs, their length of stay and the mean daily cost of remaining hospitalizations by MedDRA SOC by study region, will be used to calculate their cost.

The costs of the hospital admission for performing the kidney transplantation including the initial immunosuppressant drugs in the transplantation and the immunosuppressant drugs post transplantation, will be included and analysed as part of the costs of ESKD (see below).

*Scenario analysis in case of heterogeneity in duration of admissions between study regions*

As EMPA-KIDNEY was conducted in a four regions (Europe, North America, China and Malaysia, Japan), the length of stay (LOS) of admissions (i.e. duration of hospital admission), may differ between study regions. We will check for heterogeneity in mean LOS by MedDRA SOC between study regions. If heterogeneity is present, in a scenario analysis we will adjust the LOS of participants from regions other than Europe to those in Europe, using the ratios between mean admission LOS by MedDRA SOC category between respective regions, and report the analyses of days in hospital and costs of admissions using the adjusted LOS.

*3.2.2. <u>Study medication</u>*

Outcomes related to study medication include

- days on empagliflozin (defined below)
- cost of empagliflozin

*Study medication data*

At their randomization visit, participants allocated to empagliflozin were issued study empagliflozin 10 mg with a 7-month supply. Thereafter, at their 6 monthly visits, provided continuing study treatment remained appropriate, they were issued a further 7-month supply of empagliflozin, and any previously provided treatment was retrieved. At each study visit before discontinuation or end of trial, the approximate proportion of study treatment being taken since last visit by the participants were reported at three levels: “most”, “some”, “very little or none”.

- Most: ≥80% of the treatment since the last visit (i.e. only missed about one day a week on average);
- Some: 10-79% of the treatment since the last visit.
- Very little or none: <10% of the treatment since the last visit (i.e. only remembered to take on it on about one day a week on average).

Participants may discontinue study medication due to an adverse event, inability to perform blood tests, or consent withdrawal.

*Days on empagliflozin*

We will identify the days on empagliflozin as below:

- If participant attended the study visit
    - If “most” treatment was taken since last visit: participant was assumed on empagliflozin throughout the time period
    - If study treatment discontinued before the current visit: participant was assumed on empagliflozin from last visit to discontinuation
    - Else (very little or none, some treatment taken): participant was assumed off empagliflozin since the last visit
- If the participant did not attend the study visit, information on compliance with treatment (most, some, little or none) from the previous visit will be carried forward, together with information on empagliflozin treatment dispensed, to calculate days on study empagliflozin as noted above.

Total days on study empagliflozin will be the sum of respective days on treatment over the follow-up period.

*Cost of study empagliflozin*

The costs of study empagliflozin will be calculated based on the days on study empagliflozin and the daily cost of empagliflozin 10 mg. The daily cost of empagliflozin 10 mg will be based on unit cost per tablet of empagliflozin 10 mg (£1.31) from the national drug tariff in September 2023[5].

We will perform a sensitivity analysis including costs of all dispensed empagliflozin study medication in the study.

### *3.2.3. Concomitant medications*

Analyses related to concomitant medications include

- days on concomitant medications by category of interest
- cost of concomitant medications by category of interest

*Concomitant medication data, coding and category of interest*

Concomitant medication categories that have been hypothesized to be potentially impacted by allocation to empagliflozin will be included in the analysis. The concomitant medication categories of interest to be included in the analysis are:

- Antihypertensive treatment, including
  - RAS blockers
  - Beta blockers
  - Calcium channel blockers
  - Mineralocorticoid Receptor Antagonists
  - Other diuretics
  - Other antihypertensive treatment
- Lipid-lowering medications
- Anticoagulant or Antiplatelet therapy, including
  - Anticoagulant
  - Antiplatelet
- Diabetes treatment

In addition, days on and costs of Erythropoietin stimulating agents, Uric acid lowering and phosphate binders will be included and descriptively compared between treatment arms.

The CRF collected information on the concomitant medications taken by the patients at baseline and at each visit. The concomitant medication was coded using the Read code of the drug (SDTM code: CMCODE). By the end of EMPA-KIDNEY, 18 patients (0.5%) in the empagliflozin group and 31 (0.9%) in the placebo group had started treatment with an open-label SGLT2 inhibitor during the trial. For the purpose of this analysis plan, non-study SGLT2 inhibitor treatments will be included as part of “Diabetes treatment” concomitant medication category.

*Days on concomitant medication*

We will calculate the days on concomitant medication of interest by category as follows:

- if use of a drug was reported at two consecutive visits, the drug was used throughout the time period between the two visits;
- if use of a drug was reported in a previous visit, but not in the next visit, the drug was discontinued half-way between visits.

The total days on concomitant medication by category will be the total days over the follow-up period on any concomitant medication in the respective category.

*Costs of concomitant medication*

We will analyse the cost of concomitant medications using the cost data from the Prescription Cost Analysis (PCA) 2022/23[6], which provides the unit cost at different levels of British National Formulary (BNF) code of the prescription in England. We will map all the concomitant medications during trial follow-up period into BNF codes at the chemical substance level to derive the unit cost for the concomitant medications. We will map the Read code of the recorded concomitant medication into BNF code at the chemical substance level using the publicly available read2 to BNF mapping algorithm from the UK Biobank. The daily cost of the medication will be derived based on the cost per unit from the PCA database and the

assumption of one pill/tablet/capsule per day for each prescriptions. The total cost of included concomitant medications will be calculated based on the total days on the medication and the daily cost of the medication. For those concomitant medications not available in the UK, the average costs at BNF Chemical Substance Code or closest thereafter level in the study will be used.

### *3.2.4. Progression to CKD stages and ESKD*

*Progression to CKD stages*

Outcomes related to CKD progression include

- Time to ESKD in all the participants
- Time to CKD 5 or ESKD (whichever earlier) in participant in CKD 1-4 at entry
- Time to CKD 4, CKD 5 or ESKD in participant in CKD 1-3 at entry

CKD stage is determined at each visit based on

- first encounter of eGFR measures in the expected CKD stage at two consecutive scheduled study follow-up visits (at least 30 days apart) with entry taken from date of first such measure; or
- eGFR in the expected CKD stage measured first at the last scheduled study follow-up visit or the last scheduled visit before death (or withdrawal of consent or loss to follow-up). In this situation no confirmatory measure is required.

Time to ESKD will be derived based on the earliest date to reach ESKD (defined as dialysis or kidney transplant).

*ESKD cost*

Outcomes related to ESKD cost include

- cost of ESKD, overall and separately for dialysis (haemodialysis or peritoneal dialysis) and kidney transplant

In EMPA-KIDNEY dates of moving in and out of states of: CKD no renal replacement therapy (RRT), haemodialysis, peritoneal dialysis, and kidney transplant were recorded. We will analyse duration on each type of dialysis and kidney transplant and will use the NHS unit cost to cost them. The days on haemodialysis, peritoneal dialysis and with a functioning kidney transplant are the total days of the respective status over the study follow-up period.

Total cost of dialysis will be based on the total duration of dialysis (in years) and the annual costs of dialysis. Annual costs of dialysis will be derived based on the annual number of sessions of dialysis and the unit cost per session of dialysis. We will assume three sessions of dialysis per week for people on haemodialysis as more than 90% people on haemodialysis had such frequency in the 2020 based on the UK renal registry 24$^{th}$ annual report[7], and daily session of dialysis for people on peritoneal dialysis. Unit cost per session of haemodialysis and of peritoneal dialysis will be derived from the National schedule of reference costs 2021/2022[4]. As the unit cost is different in different types of haemodialysis and peritoneal dialysis, we will derive the weighted unit costs for haemodialysis and peritoneal dialysis across different types of haemodialysis and peritoneal dialysis based on the distribution of different types of dialysis across the UK[4].

Total costs for kidney transplant will include the costs of hospital admission for kidney transplant, and the immunosuppressive drug costs after the transplant. The costs of hospital admission for kidney transplant will be based on the recorded admission/s in the study and

their reference costs[4]. As the unit cost differ between types of kidney transplantation, we will derive the weighted unit cost across different types of kidney transplantation based on their distribution across the UK in 2021/2022[4]. The costs of immunosuppressive drugs while on transplant will only include the costs of the maintenance therapy, as costs of induction therapy are already included in the costs of the transplantation admission. The costs of immunosuppressive drugs will be based on the duration on kidney transplant, and the daily cost of maintenance immunosuppressive therapy. We will assume the maintenance immunosuppressive therapy to be the commonly used triple therapy (tacrolimus, mycophenolate mofetil, and prednisolone). Daily costs of each therapy will be calculated based on the common daily dosage (tacrolimus: 7mg/day; myophenolate mofetil: 2g/day; prednisolone: 5mg/day) and the unit costs from the most widely use generic product from the national drug tariff in September 2023 (tacrolimus: £1.11/mg [Adoport 2mg capsules]; myophenolate mofetil: £0.25/g [Mycophenolate mofetil 500mg tablets]; prednisolone: £0.01/mg [Prednisolone 5mg tablets][5].

No information was collected for patients with ESKD receiving palliative care in EMPA KIDNEY and, therefore, no palliative care costs will be included.

If necessary, costs will be inflated to year 2022 using the NHS cost inflation index (NHSCII)[8].

### *3.2.5. Quality of life*

Outcomes related to quality of life (QoL):

- QoL utility during follow-up
- QALYs

The EQ-5D-5L (EuroQol 5-Dimension 5-level) questionnaire was used to measure health-related quality of life in EMPA-KIDNEY. This instrument assesses health utilities across 5 domains, i.e. mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. The questionnaire was administered to study participants at baseline, at about 18 months follow-up and at the final follow-up visit. The recommended UK valuation method for EQ-5D-5L will be used to calculate the quality of life utility for each patient at respective visits[9].

QALYs will be calculated for each participant from randomisation into the study to final follow-up using linear interpolation between QoL utilities. For calculating QALYs, when the final follow-up QoL assessment is missing, we will impute it using the last value carried forward approach.

## 4. Population

All assessments, unless stated otherwise, will follow the principle of intention-to-treat.

We will perform subgroup analyses by:

a) baseline age: <60, ≥60<70, ≥70
b) baseline sex: male, female
c) baseline primary kidney diagnosis: diabetic kidney disease, hypertensive or renovascular disease, glomerular diseases, other or unknown
d) baseline diabetes status: presence vs. absence
e) baseline eGFR (mL/min/1.73m$^2$): <30, 30-45, ≥45
f) baseline urinary albumin:creatinine ratio (uACR, mg/g): <30, ≥30<300, ≥300<1000, ≥1000
g) baseline 5-year renal failure risk[10]: <0.05, ≥0.05<0.2, ≥0.2
h) region: Europe, North America, Japan, and China and Malaysia

## 5. Data for the analysis

Generally we will analyze the outcomes mentioned above using the within-trial period data.

The EMPA-KIDNEY Post-Trial Follow-UP (PTFU) substudy continues to follow-up a subset of consenting and surviving EMPA-KIDNEY participants for at least 2 years after the end of the within-trial period[11]. In a scenario analyses, we will use 1-year and, if available at the time of analysis, 2-year post-trial data from this substudy to re-analyze time to ESKD progression and the ESKD costs combining the within-trial and post-trial period data.

## 6. Statistical methodology

### *6.1. General approach*

For aim 1: To assess effects of empagliflozin on hospital admissions, healthcare resource use and cost, and QoL we will follow a strategy using joint modelling of the outcomes of interest and time to death to allow for the dependence between the outcomes and time to death.

For aim 2: Cost-consequence analysis of effects of empagliflozin during follow-up in EMPA-KIDNEY, the effects of allocation to empagliflozin on the respective outcomes will be evaluated using the joint models developed in aim 1 in base-case analysis, with scenario analysis using linear regression models (e.g. generalised linear or mixed-effects linear regression). For the analysis using the joint models of healthcare resources, costs and QoL, the effects of empagliflozin will be presented over the follow-up duration in EMPA-KIDNEY up to the timepoint with at least 20% of participants being followed. For example, the difference in total costs (or QALYs) will be estimated using (1) the joint models to predict the costs (QoL) and the survival probability for each participant in each trial arm; (2) calculating the total costs (QALY) by integrating the costs (QoL) over participant's survival over time; and (3) calculating the difference in the mean total costs (QALYs) across participants between trial arm. In the scenario analysis, we will present the effect of empagliflozin over the overall duration of follow-up in the trial.

### *6.2. Methods of analysis*

The null hypotheses for comparisons are that there are no differences in healthcare resource use or costs between treatment groups.

All statistical tests will be two-sided and considered significant at $p<0.05$. The conduct of multiple statistical tests of different types of resource use/costs, will be taken into account in interpretation of results.

Unless otherwise specified, all analyses will include adjustments for the variables used in the minimization algorithm, namely age, sex, prior diabetes, eGFR, urinary albumin:creatinine ratio (uACR), and region. These variables are categorical, specified as below:

- Age (year): <45, 45-55, 55-65, 65-75, ≥75
- Sex: Female, Male
- Prior diabetes: diabetes, no diabetes
- eGFR (mL/min/1.73m$^2$): <30, 30-45, 45-60, 60-75, ≥75
- uACR (mg/g): <20, 20-200, 200-500, 500-1000, ≥1000
- Region: Europe, North America, Japan, and China and Malaysia

Some or all of these variables may be removed when there is a convergence issue (see section 6.3).

### *6.2.1. Time to occurrences of hospital admission analyses*

We will use the approach specified in the EMPA-KIDNEY DAP[2] to analyse the time to hospital admission (overall and by MedDRA SOC).

A semi-parametric joint frailty model will be used. The approach will jointly model:

a) The hazard function for recurrent hospitalizations conditional on the patient-specific random frailty; and
b) The hazard function for time to death conditional on the patient-specific random frailty.

It will be assumed that the patient-specific random frailty follows a gamma distribution with mean 1 and variance θ, where θ is the correlation between the recurrent events. Piecewise constant hazards will be assumed for both hazard functions to allow estimation of the likelihood by Gaussian quadrature, with follow-up time split into five equally sized intervals. Hazard ratios for the effect of treatment on the rate of recurrent all-cause hospitalizations and the rate of death will be calculated by the model, but only the former will be formally interpreted. The joint frailty model will be adjusted for the prognostic variables used in the minimization algorithm (sex, prior diabetes and region as categorical variables and continuous standardized age, eGFR and uACR [using local screening values]).

### *6.2.2. Time to first occurrence of progression to CKD stage*

We will use the approach specified in EMPA-KIDNEY DAP[2] for analysing time to first event for the analysis of time to first occurrence of CKD progression

- Time to ESKD for all participant
- Time to CKD 5 or ESKD for all participant with eGFR >15 ml/min/1.73 $m^2$
- Time to CKD 4, CKD5 or ESKD for all participants with eGFR >30 ml/min/1.73 $m^2$

Cox proportional hazards regression adjusted for the variables used in the minimization algorithm (age, sex, prior diabetes, eGFR, urinary albumin:creatinine ratio, and region) will be used to estimate the hazard ratio associated with allocation to empagliflozin versus placebo (with the Wald chi-square statistic used to both test significance and generate an asymptotic 95% confidence interval). Any ties will be handled using Breslow's method. For any outcome where there are fewer than 10 events to reliably estimate a hazard ratio, Fisher's exact test will be used to compare the number of participants affected in each arm as per the main paper[1].

### *6.2.3. Rate/cost of healthcare resource outcomes*

The analyses of rate of healthcare resources and costs will include the analysis on the following outcomes

- Days in hospital
- Costs of hospital admissions
- Days on concomitant medication
- Costs of concomitant medication
- Costs of ESKD

Healthcare resource outcomes will be compared between all those allocated empagliflozin and all those allocated placebo.

*Base-case approach*

A shared parameter model will be used to jointly model the healthcare resource outcome using a nonlinear mixed effects model and the death outcome using a parametric survival model with the rate of the healthcare resource outcome linking both parts.

It is hypothesized that patients at higher risk of death are also at higher risk of hospital admissions/higher cost before death. However, the risk of admission/cost becomes zero following death. By jointly modelling the rate of days in hospital/cost and death, we could better capture the overall effect of empagliflozin on resource use.

The approach will jointly model:

a) The total cumulative outcome using a mixed effects poisson-log model with random effects for each patient's annual rate of resource use/costs; and
b) The time to event for death using a Weibull survival model in which the scale parameter is assumed to be linearly related to the random effects from the mixed effects model. This allows for the dependence between rate of outcome and time to death (i.e. those having more days or higher costs of healthcare resource will generally have a shorter time to death).

The shared parameter model will include treatment allocation and the prognostic variables used in the minimization algorithm (as described previously in section 5).

*Scenario analysis*

The shared parameter model is a new approach for trial-based economic analyses. In scenario analyses, we will also perform the traditional economic analyses on the healthcare resource use and costs outcomes. We will use generalized linear regression models to compare healthcare resource use and costs incurred during follow-up between treatment groups. These models will use same specifications (e.g. Poisson model) for resource use data and cost. The models will include as explanatory variables treatment assignment, the factors used in minimization algorithm and an offset variable representing duration of follow-up of individual participant.

### *6.2.4. QoL analyses*

The analyses of QoL will include the analysis on the following outcomes

- Annual rate of change in QoL or QoL slope

QoL slope will be compared between all those allocated empagliflozin and all those allocated placebo.

*Base-case approach*

We will follow a shared parameter model specification to jointly model:

a) The QoL utility during follow-up using a linear mixed effects model with random intercept and random slope for participant; and
b) The time to death using a Weibull survival model in which the scale parameter is assumed to be linearly related to the random intercept and random slope from the linear mixed effects model in a). This allows for the dependence between QoL utility during follow-up and time to death (i.e. those having QoL decreased faster will generally have a shorter time to death).

The shared parameter model will include treatment allocation, time of measurement, treatment-by-time of measurement interaction, and the prognostic variables used in the minimization algorithm (as described previously in section 5).

*Scenario analysis*

In scenario analysis, we will use a linear mixed model repeated measures (MMRM) approach including treatment allocation, time of measurement, treatment-by-time of measurement interaction, and the prognostic variables used in the minimization algorithm (in the same categories used in the minimization process). We will include patient-level random slope of QoL.

#### *6.2.5. Study medication use*

The study medication use will include the analysis on the following outcomes

- Total days of empagliflozin
- Total costs of empagliflozin

We will report the mean use/cost and their standard errors.

#### *6.2.6. Healthcare resource use*

The total healthcare resource analyses will include the analysis on the following outcomes

- Total days in hospital
- Total costs of hospital admissions
- Total days of concomitant medication
- Total costs of concomitant medication
- Total costs of ESKD

We will assess and report the differences in the healthcare resource use and costs between treatment groups on absolute scales (rather than relative differences), using shared parameters (base case) or linear regression models including treatment allocation and the prognostic variables used in the minimization algorithm (in the same categories used in the minimization process) (scenario analysis).

#### *6.2.7. Total costs analyses*

We will sum up the healthcare costs including hospital admissions, concomitant medications of interest and ESKD costs using the results generated from section 5.2.6, and report the difference in total healthcare costs between treatment groups.

#### *6.2.8. Total QALY analyses*

The difference in QALYs between treatment groups in the base case analysis will be assessed using the shared parameters model for QoL.

In a scenario analysis, we will report the difference in total QALYs between treatment groups using the QoL linear mixed model repeated measures (MMRM) approach described in the scenario analysis of QoL in 5.2.4.

### ***6.3. Convergence issues***

#### *6.3.1. Shared parameter models*

If the model fails to converge, we will try the following steps to improve the convergence:

1. For QoL analysis only: we will exclude the random intercept, and retain the random slope only in the model
2. use standardized continuous values instead of the categorical specification for continuous variables
3. if model still fails to converge, we will exclude all the minimization factors from the model

#### *6.3.2. Joint frailty models*

The following steps will be undertaken to get the model to converge. Steps are handled in a hierarchical manner as listed below:

1. Start with 50 qpoints for optimization and time scale in years
2. Reduce qpoint in steps of 5 up to a minimum of 30
3. Use qpoints = auto, using default values of qmax and qtol
4. Change time scale to months (starting with same procedure above)
5. Remove some or all of the minimization factors as covariates.

In case convergence cannot be achieved using steps above, a parametric joint Gamma-frailty model will model the recurrent event component using a Poisson distribution and model the death component using an exponential distribution, conditional on the frailty parameter for the main analysis. Individual frailties are assumed to follow a Gamma distribution. Thus, hospitalization rates follow a negative binomial distribution and times to death a Lomax distribution.

### *6.4. Subgroup analysis*

As in the main DAP, tests for heterogeneity of the effect observed in subgroups, through the inclusion of relevant interaction terms (with main effects if not already included in model) will be used to determine whether the respective effects in specific subcategories are clearly different from the overall effect.

Subgroup analysis will be performed in the sub-population mentioned in section 4, i.e. the following subgroup: (1) baseline age, (2) baseline sex, (3) baseline primary diagnosis of kidney disease; (4) baseline diabetes status, (5) baseline eGFR, (6) baseline uACR, (7) baseline 5-year renal failure risk category, and (8) region.

Generally, the subgroup analysis is performed by adding subgroup terms and the treatment*subgroup interaction terms in the main analysis. For analysis of treatment effects on the slope of the outcome (e.g. QoL), time*subgroup and treatment*time*subgroup interaction terms will also be added in the analysis. For the joint model including death as the terminal effect (e.g. hospital days and QoL), models/subgroups are dropped if there are <14 (7*number of treatment groups) death events in overall/any one category of the subgroup as implemented in EMPA-Kidney analysis[1].

For the subgroup relevant to the minimization factors already included in the model, the relevant minimization factors will be dropped:

- eGFR subgroup analyses:
  - drop eGFR minimization variable (based on local screening values)
  - add baseline eGFR (based on baseline central laboratory values at randomization)
- uACR subgroup analyses:
  - drop uACR minimization variable (based on local screening values)

  - add baseline uACR (based on baseline central laboratory values at randomization)
- diabetes subgroup analyses:
  - drop diabetes minimization variable (based on screening patient-reported history data)
  - add subgroup diabetes status (based on baseline data incorporating AE/CM/HbA1c data at randomization)
- eGFR and uACR subgroup analyses
  - drop eGFR and uACR minimization variables add baseline eGFR and uACR - central laboratory values at randomization

### *6.5. Missing data*

#### *6.5.1. Subgroup data*

Participants with missing values relevant to subgroup analyses will be included in the subgroup containing the median value. Missing eGFR values will be handled as specified in the EMPA-KIDNEY DAP and summarised here.

eGFR measured at scheduled visits will be calculated using the 2009 CKD-EPI formula, irrespective of whether the creatinine is measured centrally or locally. If multiple central eGFR measurements are available in any one scheduled follow-up period, then the eGFR closest to the ideal follow-up day will be used to define the eGFR for that scheduled follow-up visit period. The eGFR measured at the final follow-up visit will be usually be the last of the eGFR values to be included in analyses, and will be included irrespective of whether or not it is the eGFR closest to the ideal follow-up day. This may result in two eGFR values in the final scheduled follow-up period.

eGFR will be estimated from creatinine measured in the central laboratory wherever possible, but where a central laboratory eGFR measurement is expected (e.g. because a scheduled Follow-up Visit was completed whilst the participant was alive) but missing, the local blood creatinine measurement closest to the ideal follow-up day within the scheduled follow-up visit period (if one exists) will be used to estimate the eGFR in its place.

#### *6.5.2. QoL data*

All participants were expected to complete the EQ5D assessment for QoL estimation at baseline, 18-months visit and the final visit. However, many participants did not reach the 18-month time point due to the early completion of the trial. We will include all available QoL measures in the mixed effect model.

There are a few EQ5D assessments (n = 21) where some QoL domains have missing data, thus cannot be used to estimate the QoL. We will impute the missing domains using polytomous regression embedded in the r MICE (Multiple imputation by Chained equations) package with age at assessment, sex and all the EQ5D domains from all the participants before estimating the QoL for them.

### *6.6. Software*

We will use R to perform the data management for generating the analytical dataset for the final outcome analysis. We will use SAS to perform the analyses. Specifically, we will use the SAS non-linear mixed procedure (NLMIXED) to perform the joint model.

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