EMPA-KIDNEY Body Composition Monitor Substudy Data Analysis Plan (EDMS 7635)

Version History

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2 ABBREVIATIONS

Abbreviation	Definition
ACR	Albumin-to-creatinine ratio
ATM	Adipose tissue mass
BCM	Body composition monitor
BMI	Body mass index
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DPP-4	Dipeptidyl peptidase-4
ECW	Extracellular water
EDMS	Electronic document management system
eGFR	Estimated glomerular filtration rate
FTI	Fat tissue index
GLP-1	Glucagon-like peptide-1
HbA1c	Glycosylated haemoglobin
ICW	Intracellular water
LTI	Lean tissue index
LTM	Lean tissue mass
MMRM	Mixed model repeated measures
NT-proBNP	N-terminus prohormone of brain natriuretic peptide
RAS	Renin-angiotensin system
SOP	Standard operating procedure
TBW	Total body water

3 INTRODUCTION

This document provides a Data Analysis Plan for the EMPA-KIDNEY substudy, which has measured body composition of a subset of approximately 650 EMPA-KIDNEY participants recruited from the UK and Germany using bioimpedenace spectroscopy on a body composition monitor (BCM). An outline BCM data analysis plan was provided in the BCM substudy's Protocol Supplement (EDMS#6251). The purpose of this BCM Data Analysis Plan is to define, before unblinding of the treatment allocation, detail of pre-specified randomized analyses to be presented in initial publication(s) of the substudy. The nature of all analyses (randomized or observational) including those related to subsequent publications and exploratory analyses cannot be specified in detail but, where appropriate, a general analytical approach is set out. Approaches, wherever possible, will follow those set out in EMPA-KIDNEY's main data analysis plan (SOP11; EDMS#6290).

Note: this pre-specified Data Analysis Plan re-orders the priority of some of the assessments set out in the BCM substudy Protocol Supplement (EDMS#6251). Certain assessments have been moved from secondary to tertiary assessments, and a new key secondary assessment introduced. This follows a more detailed review of data whilst compiling this plan. This pre-specified Data Analysis Plan therefore supersedes the proposed assessments set out in the Protocol Supplement and prevails in the event of any discrepancies between the two documents. In addition to the pre-specified comparisons, other post-hoc analyses may be performed with due allowance for their exploratory and, perhaps, data-dependent nature.

4 KEY FLUID OVERLOAD DEFINITIONS

There is no standard nomenclature for BCM-derived fluid overload parameters in existing literature, with a range of terminology and threshold values to infer clinical significance employed. We have used the following approach to report the EMPA-KIDNEY BCM substudy.

Terminology		**Definition**
Fluid Overload		Overhydration in litres, computed as the difference between expected (based upon weight and body composition) versus measured extracellular water (ECW) volume (1), with positive values representing excess fluid. Fluid Overload = $ECW_{measured}$ - $ECW_{expected}$.
Relative Fluid Overload		Overhydration index* relative to measured ECW volume, expressed as a percentage (2). Relative Fluid Overload = Fluid Overload ÷ $ECW_{measured}$.
Clinically Significant Fluid Overload	Moderate	Relative Fluid Overload >7% to ≤15% [where 7% reflects the 90th percentile in a healthy reference population and is approximately equivalent to absolute Fluid Overload of +1.1L (3)].
	Severe	Relative Fluid Overload >15% [which represents the highest quartile in a haemodialysis reference population (1, 2); approximately equivalent to absolute Fluid Overload of +2.5L (2-5)].

**Although scientific literature has used the term "overhydration index" to refer to both absolute Fluid Overload in litres and Relative Fluid Overload (6, 7), we consider it to most accurately describe overhydration indexed to ECW.*

5 BASELINE CHARACTERISTICS

In order to assess balance of baseline characteristics between randomized arms of BCM substudy, the following variables recorded at Randomization (or at Screening) will be presented for each of the empagliflozin and placebo groups. All participants with at least one valid BCM measurement will be included, with missing baseline BCM values imputed using methods set out in section 7.1.

Note that these are a subset of the characteristics pre-specified in the main Data Analysis Plan (SOP11; EDMS#6290) plus other measures of anthropometry and BCM measurement variables. Categories will be consistent with those from the main trial publications or subgroup analyses:

a. History of prior disease:
    i. Diabetes mellitus (presence *vs* absence);
    ii. Self-reported heart failure (presence *vs* absence);
    iii. Primary renal diagnosis (diabetic kidney disease, hypertensive/renovascular disease, glomerular disease, other or unknown[1])
b. Patient characteristics;
    i. Age (continuous and categorised: <60; ⩾60 <70; ⩾70 years);
    ii. Sex (male *vs* female);
    iii. Race (White, Black/African American, South Asian, Southeast Asian, Mixed or Other);
    iv. Smoking status (ever smoked regularly at Randomization, yes *vs* no);
    v. Weight in kg*;
    vi. Body mass index (BMI) (continuous and categorised: <25; ≥25 <30; ≥30 kg/m^2);
    vii. Waist-to-hip ratio*;
    viii. Extracelllular water (ECW) in litres*;
    ix. Intracellular water (ICW) in litres*;
    x. Fluid Overload in litres*;
    xi. Relative Fluid Overload (%)*;
    xii. Clinically Significant Fluid Overload (%, presence *vs* absence)*;
        - Moderate

[1] Other includes tubulointerstitial disease, familial/hereditary nephropathies, other systemic disorders and miscellaneous renal disorders. Glomerular disease is subcategorised as follows: focal segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy, minimal change disease and other glomerular disease.

- Severe (see section 4 for definitions)

xiii. Lean tissue index (LTI) (lean tissue mass [LTM] indexed to height) *;
xiv. Fat tissue index (FTI) (adipose tissue mass [ATM] indexed to height) *;
xv. Systolic blood pressure (continuous and categorised: <130; ≥130 <145; ≥145 mmHg);
xvi. Diastolic blood pressure (continuous and categorised: <75; ≥75 <85; ≥85 mmHg);

c. Laboratory values at Randomization:
   a. CKD-EPI estimated glomerular filtration rate (eGFR) (continuous and categorised: <30, ≥30 <45, ≥45 mL/min/1.73m^2 estimated from central enzymatic creatinine [or local creatinine where central value unavailable])
   b. Urinary albumin:creatinine ratio (ACR): (continuous and categorised: <30, ≥30 ≤300, >300 mg/g)
   c. Glycosylated haemoglobin (HbA1c) (continuous and categorised: <39 [normoglycaemia], ≥39<48 [pre-diabetes], ≥48<75 [well-controlled diabetes], ≥75 [poor glycaemic control] mmol/mol, or missing
   d. N-terminus prohormone of brain natriuretic peptide (NT-proBNP) (continuous and categorised: <110, ≥110 <330, ≥330 ng/L)
   e. Haematocrit (continuous and categorised: <37%; ≥37% <41%; ≥41%)
d. Medication use at randomization:
   i. RAS inhibition (yes *vs* no);
   ii. Diuretics (yes *vs* no, and analyses by type [loop *vs* thiazide *vs* mineralocorticoid receptor antagonist *vs* other potassium-sparing].
   iii. Antidiabetic medications (yes *vs* no, and analyses by type [biguanide *vs* sulphonylurea *vs* insulin *vs* DPP-4 inhibitor *vs* GLP-1 agonist *vs* other]

* continuous and categorized into approximate thirds of the distribution.

In general, baseline characteristics presented in publications will include all those listed above, with those provided in main versus subsidiary tables selected based upon relevance to the publication. For continuous variables, mean (standard deviation) will be presented unless the variable has a skewed distribution, in which case median (interquartile range) will be used. For all categorical variables, the number and percentage of participants in the category will be presented. All possible categories will be displayed, zero-filled where necessary, the category 'missing' will only be displayed (e.g. in footnotes) if there are actually missing values.

6 DEFINITIONS OF KEY RANDOMIZED ASSESSMENTS

BCM measurements were specified to be performed at Randomization, 2 and 18 months of Follow-up Visits (EDMS#6251). At these visits, weight, waist circumference, and hip circumference were measured together with blood and urine for central analysis and storage. The COVID-19 pandemic caused a substantial proportion of face-to-face Follow-up Visits to be delayed, however BCM measurements were permitted at later attended Follow-up Visit appointments, as outlined in the table below. Unless otherwise specified, all analyses will involve an intention-to-treat comparison among all randomized participants with at least one valid BCM measurement during Follow-up of the effects of allocation to empagliflozin versus placebo during the scheduled treatment period (i.e. all participants will be included irrespective of whether they take none, some or all of their allocated treatment) (8-10). Handling of missing valid BCM measurements is described in section 7.1.

Scheduled Follow-up Visits relative to the Randomization Visit date

Trial visit number	Follow-up month	Follow-up period	Ideal Follow-up day
1	2	≥30, <400 days	60 days
4	18	≥400 days, until Final Follow-up*	540 days

* Assume <680 days for maximum window for purposes of calculating weighting.

6.1 Hypotheses

For all statistical tests (other than tests for heterogeneity or trend), the null hypothesis will be that the effect of allocation to empagliflozin on the parameter of interest (e.g. Fluid Overload) in the target population is the same as the effect of allocation to placebo (and hence the alternative hypothesis will be that the effect of allocation to empagliflozin is not the same as the effect of allocation to placebo).

6.2 Primary randomized assessment

The primary assessment will be the effect of allocation to empagliflozin on mean absolute Fluid Overload in litres. Effects on Relative Fluid Overload (overhydration indexed to ECW, expressed as a percentage) will be presented alongside. Effects will be averaged over the two Follow-up time points (with weights proportional to the amount of time between visits, see section 7.2.1), adjusted for Randomization Fluid Overload values. The details of analysis methods for the primary assessment are described in section 7.2.1.

6.3 Key secondary randomized assessment

The key secondary composite outcome combines clinical outcome data with BCM measurements. Important data on fluid overload captured by BCM measurements is missed when remote Follow-up visits are necessary (e.g. as a result of the COVID-19 pandemic) or after death, so the composite outcome serves to capture all recorded data on fluid overload and its clinical consequences (whether measured by BCM or reflected in reported adverse events). The key secondary assessment is time-to-first development or worsening of Clinically Significant Fluid Overload. The composite outcome is defined as:

- Death from Heart Failure;
- Hospitalization for Heart Failure (as defined for the main trial analyses in SOP11; EDMS#6290); or
- Development of moderate Clinically Significant Fluid Overload (defined as >7% to ≤15% Relative Fluid Overload) among those without any Clinically Significant Fluid Overload at baseline; or
- Development of severe Clinically Significant Fluid Overload (defined as >15% Relative Fluid Overload) among those without this outcome at baseline.

The analysis method is described in section 7.2.2.

6.4 Other secondary randomized assessment

The other secondary assessment is to test whether the effects of empagliflozin 10mg versus matching placebo on Fluid Overload vary with time – in addition to the primary randomized assessment, analyses will be presented for the separate early (2-month) versus late (18-month) time points. The analysis method is described in section 7.2.3.

6.5 Tertiary randomized assessments including subgroup analyses

Tertiary assessments include:

i. Whether any effects of empagliflozin 10mg versus matching placebo are modified by baseline factors listed in section 5 for the primary assessment (absolute Fluid Overload). Subgroups based on sex, diabetes status, NT-proBNP, and eGFR will be the key subgroups and will be emphasised in presentation and interpretation. The sensitivity of subgroup assessments to indexing to ECW will be assessed by repeating subgroup analyses for the outcome of Relative Fluid Overload.

ii. The effects of empagliflozin 10mg versus matching placebo overall, and also early versus later during follow-up on:

a. Extracellular water (ECW)
b. Intracellular water (ICW)
c. Lean tissue index (LTI) (lean tissue mass [LTM] indexed to height)
d. Fat tissue index (FTI) (adipose tissue mass [ATM] indexed to height)
e. Body weight
f. BMI
g. Waist circumference
h. Hip circumference
i. Waist-to-hip ratio

iii. The effects of empagliflozin 10mg versus matching placebo on the four separate components of the key secondary outcome of development or worsening of Clinically Significant Fluid Overload.

iv. The effects of empagliflozin 10mg versus matching placebo on regression of Clinically Significant Fluid Overload from Severe (>15%) to Moderate (>7%); Severe to normal (≤7%); or Moderate to normal.

The analysis method for tertiary assessments is described in section 7.2.4.

6.6 Additional exploratory analyses

Additional exploratory analyses are planned however these are beyond the scope of this DAP and will be described in detail elsewhere.

7 STATISTICAL METHODOLOGY

7.1 Handling of missing and extreme values

Participants with a missing baseline BCM measurement will still be included in analyses if subsequent BCM measurements are obtained within the 2- and/or 18-month Follow-up windows. Missing baseline BCM measurements will be imputed with the average observed value (in both treatment groups combined). Sensitivity analyses will be performed limited to participants with complete baseline BCM data. Participants with missing baseline values relevant to subgroup analyses will be included in the subgroup containing the average value (or the most frequent category for a binary variable). Missing Follow-up BCM measurements including Fluid Overload at 2 and 18 months will be handled in the mixed model repeated measures (MMRM) approach (as outlined in section 7.2.1).

7.2 Methods of analysis

7.2.1 Primary randomized assessment

Absolute Fluid Overload in litres will be analysed as a continuous variable. Extreme outliers (defined as >2 standard deviations from the mean) will be reviewed prior to unblinding to assess data quality and plausibility (see Appendix section 8.1). These analyses will be completed before any randomized comparisons are conducted. Differences in Fluid Overload between treatment groups will be assessed using a mixed model repeated measures (MMRM) approach adjusted for the elements included in the minimization algorithm which determined treatment allocation (age, sex, prior diabetes, eGFR, and urinary ACR [but not region as the BCM substudy was only conducted in Europe]).

The primary assessment will focus on a weighted average of the values at the two Follow-up time points with weighting based on the relative size of each Follow-up window as set out in section 6. As the first Follow-up window (2-month Follow-up) is 370 days (days 30-400 post-Randomization) and the second window (18-month Follow-up) assumed to be 280 days (days 400-680 post-Randomization), this effectively weights information at the first Follow-up visits as 55% compared to 45% at the second. This is appropriate as we hypothesise that there will be a greater effect of empagliflozin versus placebo on Fluid Overload at 2 months versus 18 months as the effect of empagliflozin on Fluid Overload is expected to develop rapidly and diminish over time. Additionally, changes to other medication which can influence fluid balance may occur over time. Time will be included in the model as a categorical variable to avoid assuming a linear association between treatment allocation and Fluid Overload over time. The model will include fixed, categorical effects of treatment allocation, treatment-by-time interaction, and the prognostic variables used in the minimization algorithm (in the same

categories used in the minimization process) along with continuous effects of baseline (randomization) measurements and baseline-by-time interaction. The within-person error correlations will be assumed to be unstructured.

7.2.2 Assessment for key secondary randomized assessment

Time-to-first event analyses will use adjusted Cox regression. The general statistical methods and approaches to subgroup analyses are set out in the main Data Analysis Plan (SOP11; EDMS#6290). Follow-up for the clinical components of the composite outcome will be censored according to the main Data Analysis Plan. Follow-up for the BCM-derived components of the development or worsening of Fluid Overload outcomes (see section 4 for definitions) will be censored on the day after the last valid BCM measurement (but these individuals may remain at risk of clinical outcomes) or at death/withdrawal of consent.

7.2.3 Other secondary randomized assessment

The effect of treatment allocation on Fluid Overload separately at 2 and 18 months (see section 6.4) will be analysed using the same MMRM approach outlined in 7.2.1.

7.2.4 Tertiary randomized assessments including subgroup analyses

The same MMRM approach outlined in section 7.2.1 will be used for tertiary assessments (i) and (ii) as described in section 6.5. Tertiary assessment (i) is an analysis of the primary outcome by subgroup. Subgroup analysis will be performed by fitting relevant interaction terms for subgroups in the MMRM model with the aim of assessing whether the proportional effects in specific subgroups are statistically different from the overall effect. Interpretation will take into account the number of subgroups assessed as well as biological rationale. Tertiary assessment (ii) will use the same MMRM approach as for the primary assessment (section 7.2.1). Tertiary assessments (iii) and (iv) which analyse effects of treatment allocation on the components of the composite key secondary outcome and regression of Clinically Significant Fluid Overload will be analysed according to the same time-to-event approach outlined in section 7.2.2.

Further technical documentation to accompany this Data Analysis Plan may also be added as an appendix, if additional methodological details for the approaches described in section 7 are found to be required.

8 APPENDIX: DEFINITION OF VALID BCM MEASUREMENTS AND DATA HANDLING CONSIDERATIONS

8.1 Definition of a valid BCM measurement

To be included in analyses, an EMPA-KIDNEY participant must have at least one valid BCM measurement during Follow-up and been allocated to empagliflozin 10mg or matching placebo. To be included in analyses, each BCM measurement must have a corresponding weight measurement recorded at the same visit, from which BCM parameters can be derived according to the procedure set out in EDMS#7248.

Validity of BCM measurements will be assessed, prior to unblinding. Measurements with an absolute Fluid Overload value more negative than -5 litres will be excluded due to implausibility[1]. Measurements with a Q value[2] of <80 (site staff were trained to repeat BCM measurements if the Q value was <80; EDMS#6240) will be identified for visual inspection of the associated Cole-Cole plot[3] to assess data quality and determine inclusion in analyses. Two observers blind to treatment allocation will independently assess Cole-Cole plots by visual inspection, applying pre-specified criteria (outlined in section 8.4), with any differences resolved by consensus discussion.

Information on completeness of valid BCM data at each visit (i.e. number of participants with at least one valid BCM measurement at each visit, no valid BCM measurement but at least one invalid measure, or no BCM measurement) will be presented in the substudy CONSORT flow diagram. Statistical comparisons by treatment will be presented for the following parameters:

- The distribution of Q values for measurements included in the main comparison and sensitivity analyses
- The distribution of time-to-measurements from Randomization for each Follow-up window.

[1] In pilot work, Cole-Cole plots were reviewed for all measurements with absolute Fluid Overload values >2 standard deviations from the mean in a preliminary dataset to inform this cut-off. Values more negative than -5 litres were consistently associated with poor quality Cole-Cole plots. Conversely, outlying positive values were found to consistently have good quality Cole-Cole plots (and are considered plausible results).
[2] The Q score is an assessment of data quality generated by the BCM where 100 is a perfect Q value. In pilot work, a random subset of 50 measurements with a Q score ≥80 were selected for Cole-Cole plot review. Q scores above this threshold were confirmed to be a reliable indicator of good data quality in the cohort.
[3] The Cole-Cole plot generated by the BCM device fits a curve to the measured impedance data and defines the extracellular and intracellular resistances upon which all body composition data are based. Visual inspection of Cole-Cole plots identifies artefact within the impedance data.

8.2 Handling multiple BCM measurements

8.2.1 Multiple valid BCM measurements at the same visit

In all analyses, if more than one valid BCM measurement is available at a single Follow-up visit (i.e. date), the measurement with the highest Q value will be used and additional measurements ignored. In the situation where >1 valid measurements are obtained with an identical Q value, the first measurement will be used.

8.2.2 Multiple valid BCM measurements within a Follow-up window

In all analyses, if valid BCM measurements are made on more than one day within a Follow-up period, then the valid BCM measurement made on the day nearest the ideal follow-up day will be used and other BCM measurement excluded (see section 6 for Follow-up days). In the situation where >1 valid BCM measurements are obtained within the Follow-up window on dates which are equidistant from the ideal Follow-up date, a mean value will be calculated and used in analyses. This is considered a more scientifically robust approach in this unique situation due to the hypothesised interaction of time in the association between treatment allocation and Fluid Overload which means that selecting one or other equidistant measurement on the basis of Q values could introduce bias.

8.2.3 Multiple measurements at different visits on a single BCM card

Where data for two separate visits is recorded on a single BCM card, valid BCM results will be derived for the separate visits, wherever possible.

8.3 Data processing: BCM variables

The BCM provides measurement of:

- Extracellular water (ECW) resistance (denoted as R_e)
- Intracellular water (ICW) resistance (denoted as R_i)

BCM data are downloaded to study-specific laptops in a .pat file format and imported into a Microsoft Excel™ spreadsheet according to the procedure set out in EDMS#7248.

The following data are extracted from the analysis database to allow processing of the BCM data:

- Age, recorded in whole years at the time of each BCM measurement
- Weight, measured in kilograms, at the time of each BCM measurement
- Height, measured in centimetres, at Randomization
- Sex, recorded as male or female, at Randomization

along with Re and Ri reported by the BCM

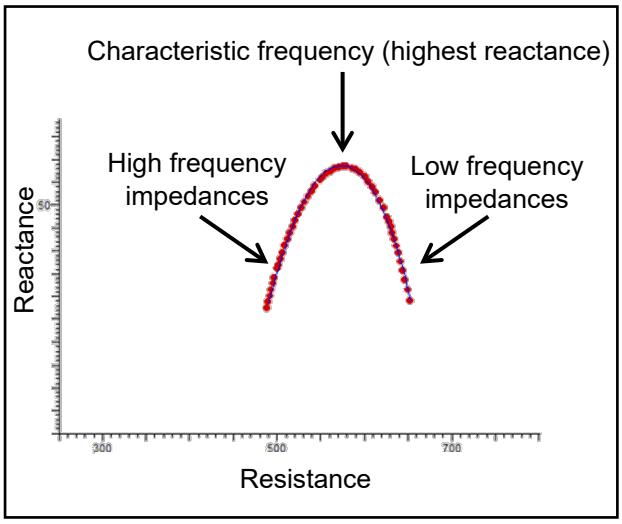
Standard formulae will be applied to methodology described by Moissl and Chamney et al (11, 12) .[1] to derive the following:

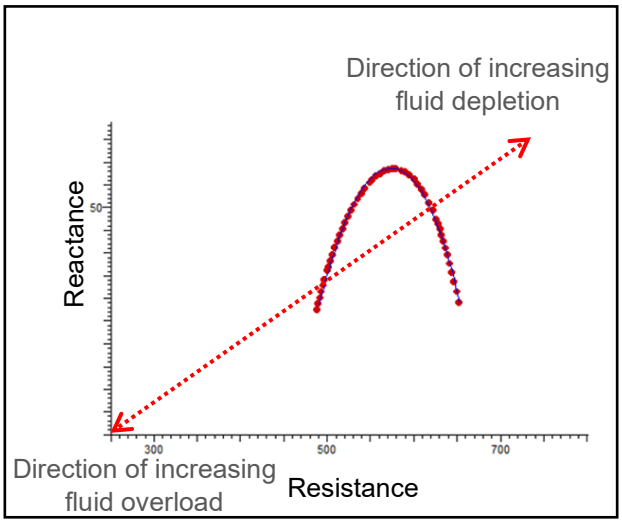
- Body mass index (BMI) in kg/m^2 using height and weight
- Extracellular water (ECW) in litres
- Intracellular water (ICW) in litres
- Total body water (TBW) in litres, by addition of ECW and ICW values
- Absolute Fluid Overload in litres
- Relative Fluid Overload (indexed to ECW), expressed as %
- Lean tissue index (LTI)
- Fat tissue index (FTI)

[1] Methods will use different coefficients to those available in published the current literature (coefficients which have been shared with permission).

8.4 Criteria for rejecting BCM measurements by Cole-Cole plot visual inspection

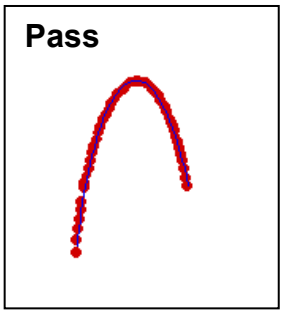
The two diagrams below provide a basic interpretation of the Cole-Cole plot:



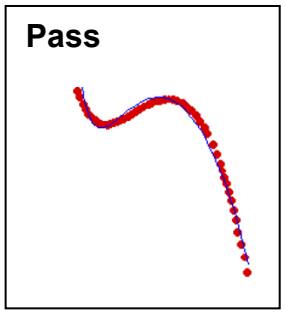


When manually reviewing Cole-Cole plots generated by the BCM for quality assurance, the following rule will be used to classify measurements as having poor data quality.

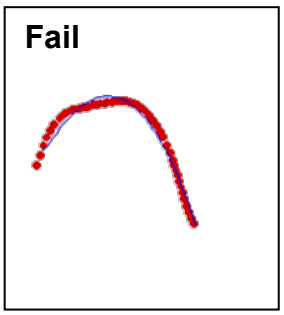
KEY CRITERION: In the opinion of the observer blind to treatment allocation, a good quality Cole-Cole plot should have the basic structure of a parabola, ignoring any artefacts at the high and low frequency end, and the plotted blue curve should closely fit the raw data red.
Examples of good ("pass") and poor ("fail") quality bioimpedance data are provided below:



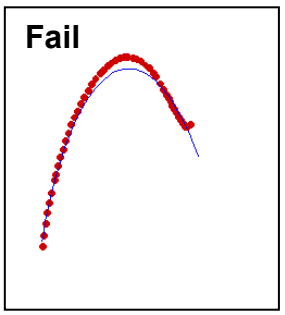
Parabola with good fit of plotted curve against raw data



Ignoring artefact at high frequency, acceptable parabola with good fit



Raw data is not parabolic in shape & consequently poor fit



Unacceptable fit of plotted curve against raw data

Note: review of the Cole-Cole plot is not affected by the height or width of the plot, length of either end of a parabola, nor its position in the plot region.

8.5 Sensitivity analyses

Data quality assessment outlined in section 8.1 will be used to determine data inclusion in the primary analysis. Sensitivity analyses will also be conducted to assess the impact of the data quality assessments on the effects of empagliflozin versus placebo on the primary randomized assessment. These include analyses:

1. Of all single BCM measurements, irrespective of quality assessment or outlying values (i.e. the complete “unreviewed” set)
2. Restricted to single BCM measurements with a Q value ≥80 (i.e. a stricter criterion than the primary approach)

The criteria outlined in section 8.1 are thought to represent the optimal data quality assessment procedure to determine inclusion in the primary analysis and these sensitivity analyses represent the two alternative most extreme approaches.

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