A multi-country time and motion study to describe the experience of clinicians, patients and their caregivers during the treatment of Fabry Disease with Enzyme Replacement Therapy with agalsidase alpha and agalsidase beta.

# Statistical Analysis Plan

**Prepared for:**

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| Date: | 29th March 2021 |
| Version: | SAP v2.0 |



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**List of abbreviations**

| Abbreviation | Definition |
|---|---|
| CI | Confidence interval |
| CSI | Caregiver Strain Index |
| eGFR | Estimated glomerular filtration rate |
| ERT | Enzyme replacement therapy |
| FD | Fabry Disease |
| HCP | Healthcare Professional |
| HRQoL | Health-related quality of life |
| IQR | Interquartile range |
| LVMi | left ventricular mass index |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SF-12 | 12 Item Short Form Survey |
| SF-36 | 36 Item Short Form Survey |
| WHO-5 | World Health Organization-5 Wellbeing Index |
| WPAI | Work Productivity and Activity Index |
| WPAI-CG | Work Productivity and Activity Index: Caregiver |

# 1. ANALYSIS AIM AND OBJECTIVES

## 1.1 Primary Objective

To quantify the total time spent by HCPs (Health Care Professional) in the preparation and administration of a single dose of ERT (with agalsidase alfa and agalsidase beta) in patients with Fabry disease (FD).

## 1.2 Secondary Objectives

- To quantify the total patient time (hours/minutes), their costs (i.e. out of pocket expenses) and work-related absence associated with attendances for the administration of a single dose of ERT (with agalsidase alfa and agalsidase beta) in patients with FD.

- To quantify the total caregiver time (hours/minutes), their costs (i.e. out of pocket expenses) and work-related absence associated with accompanying a patient with FD for their administration of a single dose of ERT (with agalsidase alfa or agalsidase beta).

- To describe patient-reported HRQoL (measured by the 12 Item Short Form Survey [SF-12]), wellbeing (measured by the World Health Organization-5 Wellbeing Index [WHO-5]), levels of fatigue (measured by a bespoke Fatigue Likert scale) and work productivity (measured by the Work Productivity and Activity Index [WPAI] questionnaire) in patients with FD treated with ERT.

- To describe work productivity (measured by the WPAI for caregivers [WPAI:CG]) and the strain of care provision (measured by Caregiver Strain Index [CSI].

## 2. STATISTICAL ANALYSIS

OpenHealth will carry out the statistical analysis for this project on behalf of Amicus. Analysis will be performed in R statistical software version 3.4.1, Stata™ (StataCorp LLC) version 14 and/or Microsoft Excel™.

### 2.1 Populations for analysis

Patients with FD who are receiving ERT and their caregivers from approximately 12 specialist centres in four countries (Taiwan, Turkey, Brazil and Japan) will form the sample for this study. In total, this study will have 240 ERT episodes, which includes 60 ERT episodes (30 for agalsidase alfa and 30 for agalsidase beta) in each participating country. Ideally, a maximum of two ERT administration episodes will be observed per patient; as such, at least 30 patients are expected to be enrolled in each country. For countries with limited FD patient numbers, a review of episodes of care observed will be completed on an ongoing basis. It may be determined that it is possible to observe three episodes per patient in these circumstances, however only two episodes will be observed per patient wherever possible.

### 2.2 Key definitions

**Episode of care:** An episode of care is an element or part of the care or treatment pathway which is being studied or measured. For the purpose of this study, an episode of care will constitute all healthcare professional (HCP) activities involved in the preparation and administration of a single dose of enzyme replacement therapy (ERT) with agalsidase alfa and agalsidase beta, including ERT (and pre-medication) preparation, pre- and post-administration assessment, pharmacy and clinic activities, and any follow up activities.

**Caregiver:** in the context of this study a caregiver is defined as an individual aged 18 years or over who has a personal relationship with and provides informal (unpaid) care, support or assistance to someone diagnosed with Fabry Disease, and accompanies them to the hospital or treatment centre for ERT administration on one or more occasion during the study data collection period. For example, this may be a parent, spouse/ partner, son/ daughter, other relative, neighbour or friend.

### 2.3 Missing Data

Where dates are ambiguous because of missing day and/or months, standard imputation will be applied: where day is missing the 15th of the month will be assumed; where both day and month are missing the 1st July will be assumed.

For other missing data, the affected analyses will be conducted using only the results of those patients/episodes with data available and the number included in each analysis will be stated.

The number of patients or caregivers with data missing will be reported for each study variable.

### 2.4 Sample Size Justification

The target sample size for the time and motion evaluation undertaken as part of this study is 240 ERT episodes, including 60 ERT episodes (30 for agalsidase alfa and 30 for agalsidase beta) in each participating country. Ideally, a maximum of two ERT administration episodes will be observed per patient; as such, at least 30 patients are expected to be enrolled in each country. For countries with limited FD patient numbers, a review of episodes of care observed will be completed on an ongoing basis. It may be determined that it is possible to observe three

episodes per patient in these circumstances, however only two episodes will be observed per patient wherever possible.

For the questionnaire evaluation, approximately 120 patients and 20 caregivers will be expected to fill questionnaire sets (approximately 30 patients' and 5 caregivers' questionnaire sets per country).

### 2.5 Analysis for descriptive endpoints

This study is designed to be descriptive in nature; there is no *a priori* hypothesis to be tested and therefore no comparisons between patient subgroups or treatments will be made. Distributions and descriptive statistics of central tendency (medians and arithmetic or geometric means) and dispersion (standard deviation [SD], interquartile range [IQR], range) will be presented for quantitative variables. Categorical variables will be described with frequencies and percentages; where appropriate, distributions, modes, medians, IQR and range will be reported. Where appropriate, 95% confidence intervals (95% CI) will also be presented for means and estimates of proportions. Ordinal variables will be evaluated using either frequencies and percentages or medians and IQR or both depending on the number of possible values for the variable.

Analysis for validated instruments will adhere to the licensed scoring manual. Item and domain scores (if relevant) will be presented.

All percentages will be reported to the nearest whole number; therefore, in reporting study results in tables, figures and associated text, percentages may not add up to 100% due to rounding. For total group/subgroup sizes of less than 10, percentages will not be reported, except under exceptional circumstances. Consideration will be given during data analysis as to whether reporting any of the planned analyses may identify individuals from combinations of variables occurring in very small groups; to preserve participant anonymity such results may be suppressed in the study report and any materials intended for publication.

## 2.6 Analysis of the primary objectives

**Objective 1**

**To quantify the total time spent by HCPs in the preparation and administration of a single dose of ERT (with agalsidase alfa and agalsidase beta) in patients with FD.**

| Endpoint and variables required | Description of analytical approach |
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| The total time spent by HCPs (physician / nurse / nurse assistant or healthcare assistant / pharmacist / pharmacy assistant / other ) in the preparation and administration of a single dose of ERT in patients with FD | The total time spent will be treated as quantitative variables and will be summarized with mean,sd etc, as per described in section 2.5. The summary statistics will be produced separately for each country and by ERT product (agalsidase alfa or agalsidase beta). |
| Episode setting (hospital / infusion centre / primary healthcare centre / primary healthcare centre (preparation and set-up) with home infusion) / other (specify) | The frequency and percentages will be provided for each of these categorical variables. |
| ERT product administered: agalsidase alfa (Replagal®, Shire or biosimilar) or agalsidase beta (Fabrazyme®, Sanofi Genzyme or biosimilar)<br>○ ERT dose administered.<br>○ Pre-medications administered | |
| **Secondary Endpoints**<br><br>Summary measures of the time spent by HCPs on the following tasks associated with the preparation and administration of a single dose of ERT (with agalsidase | The total time will be calculated by summing the difference in start and end time of these activities. This will be summarized using mean, sd, median and IQR as per section 2.5. |

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| alfa or agalsidase beta) in patients with FD: | |
| Pre-administration patient consultation:<br>○ Time patient arrived<br>○ Time patient left clinic | Time patient left – Time patient arrived<br>End time – Start time |
| Start and end time of patient consultation with HCP for pre-treatment assessment. | End time – start time |
| Start and end time of prescription writing (if additional to consultation time with patient). | End time – start time |
| Start and end time of pre-administration clinical document-tation (if additional to consultation time with patient). | End time – start time |
| **Infusion (and pre-medication) preparation activities:**<br>Start and end time of infusion (and pre-medication) preparation activities (note: the following activities [as appropriate] will be included in the total time, but the time for each separate activity will not be recorded]: pre-dispensing prescription review, label generation, collation of items prior to assembly, assembly of item/drug reconstitution, labelling of containers, accuracy check, prescription delivery). | Time patient left – Time patient arrived |
| **ERT Infusion Procedure (and pre-medication) administration:** | End time – Start time |

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| Time patient arrived in clinic for ERT administration to begin<br><br>Time patient left clinic following completion of ERT administration<br><br>Start and end time of pre-medication administration.<br><br>Start and end time of ERT infusion.<br><br>Start and end time of HCP activity for administration of IV agalsidase alfa or agalsidase beta (including administration of pre-medications).<br>Start and end time of HCP activity for patient monitoring during agalsidase alfa or agalsidase beta infusion<br><br>**Post-infusion administration assessment and documentation:**<br><br>Start and end time of HCP activity for post-treatment patient assessment / monitoring.<br><br>Start and end time of HCP activity for completion of clinical documentation.<br><br>**Other ERT-administration related activities**<br><br>Start and end time of HCP activity for any other ERT administration related activities (specify). | End time – Start time<br><br>End time – Start time<br><br>End time - start time<br><br>End time – start time<br><br>End time – start time<br><br>End time – Start time |
| **Secondary Objective 1**<br><br>**To quantify the total patient time, costs (i.e. out-of-pocket expenses) and work-related absence associated with attendances for the administration of a single dose of ERT (with agalsidase alfa or agalsidase beta) in patients with FD.** | |
| **Summary measures of the total patient time associated with** | |

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| **attendance for the administration of a single dose of ERT (with agalsidase alfa or agalsidase beta) in patients with FD.**<br><br>Time spent travelling to and from the hospital or treatment centre<br><br>○ Time left home/work to travel to hospital or treatment centre<br><br>○ Time arrived at hospital or treatment centre<br><br>Time spent collecting ERT from pharmacy (where relevant)<br><br>Time from arrival in hospital/treatment centre to departure<br><br>○ Time from arrival in hospital/treatment centre to start of ERT infusion<br><br>○ Start and end time of ERT infusion.<br><br>○ Time left hospital or treatment centre to travel back to home/work<br><br>○ Time arrived back at home/work.<br><br>In addition, if the patient started/delivered their ERT infusion at home following set-up at a primary healthcare centre, the following will also be included in the total patient time | The difference between two time points will be calculated in minutes and will be summarized as per section 2.5 for quantitative variables for the following measures.<br><br>Time left home – Time arrival at hospital<br><br>Time arrived – Time start of ERT<br><br>End time – Start time<br><br>Time arrived at home – Time left hospital |

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| Duration of ERT infusion and any home-based post-administration activities.<br>○ Start and end time of ERT infusion<br>○ Start and end time of any post-administration activities. | End time – start time<br><br>End time – start time |
| Time spent travelling to and from treatment centre after ERT infusion (only if patient returned to treatment centre after ERT infusion)<br>○ Time left home/work to return to hospital or treatment centre (if relevant)<br>○ Time arrived back at hospital or treatment centre (if relevant) | Time left – Time arrived |
| Time spent at treatment centre after ERT infusion.<br>○ Time left hospital or treatment centre to travel back to home/work<br>○ Time arrived back at home/work | Time arrived back at hospital – Time left hospital/ treatment centre<br><br>Time left – Time arrived back at home/ work |
| Summary measures of the total cost to patients (i.e. out-of-pocket expenses) associated with attendance for the administration of a single dose of ERT (to include the costs of travel / parking / subsistence / other costs). | |

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| • Did patient take any time off work to attend this ERT episode? If yes, number of paid / unpaid hours absent from work.<br><br>• Proportion of patients with work absence due to attendance for this ERT episode and number of paid / unpaid hours absent. | Frequency and percentages will be used to summarise the proportion of patients with work absence due to attendance for this ERT episode.<br><br>Number of paid/ unpaid hours from work will be summarised using mean, sd, median and IQR as per section 2.5. |
| Distribution of patient employment status and whether the patient attended the ERT administration visit accompanied by a relative/caregiver or alone.<br><br>• Patient employment status (employed full time / employed part time / unemployed / retired / student / home-maker)<br><br>• Were they accompanied to the hospital or treatment centre (by a relative or caregiver) or did they attend alone (accompanied / alone) | These categorical variables will be summarized using frequency and percentages as per section 2.5. |
| Costs (i.e. out-of-pocket expenses) incurred by the patient that were directly related to this ERT administration episode (to include costs of travel / parking / subsistence / any other costs). | Costs will be summarized using mean, sd, median and IQR as described in section 2.5. |
| **Secondary objective 2**<br><br>**To quantify the total caregiver time costs (i.e. out-of-pocket expenses) and work-related absence associated with accompanying a patient with FD for the administration of a single dose of ERT (with agalsidase alfa or agalsidase beta).** | |

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| **Summary measures of the total caregiver time associated with accompanying a patient with FD for the administration of a single dose of ERT (with agalsidase alfa or agalsidase beta).**<br><br>Demographics for caregiver<br><br>○ Sex<br>○ Age category<br>○ Has FD or not<br>○ Employment status<br>○ Relationship to patient<br>○ Type of care<br>○ Frequency of care | The frequency distribution and percentage for each category of the demographic variable will be given. |
| ○ Time left home/work to travel to hospital or treatment centre<br><br>○ Time arrived at hospital or treatment centre<br><br>○ Time of start of ERT infusion<br><br>○ Time left hospital or treatment centre to travel back to home/work<br><br>○ Time arrived back at home/work. | The difference between these two time points in minutes will be summarized as in section 2.5 for quantitative variables. |
| **If the patient started their ERT infusion at home following set-up at a primary healthcare centre, the following will also be collected (if the caregiver was involved in the activity)**<br><br>○ Start and end time of ERT infusion | The difference between start and end time (in minutes) of these will be calculated and summary statistics will |

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| ○ Start and end time of any post-administration activities.<br><br>○ Time left home/work to return to hospital or treatment centre (if relevant and if accompanied by caregiver)<br><br>○ Time arrived back at hospital or treatment centre (if relevant)<br><br>○ Time left hospital or treatment centre to travel back to home/work<br><br>○ Time arrived back at home/work | be calculated by treating as quantitative variables as given in section 2.5. |
| ○ Did caregiver take any time off work to attend this ERT episode? If yes, number of paid / unpaid hours absent from work. | Whether the caregiver took time off or not will be depicted as frequency and percentages. The number of paid/unpaid hours will be summarized as given in section 2.5 for quantitative variables. |
| ○ Number of hours worked during ERT infusion (if relevant). | The summary statistics for quantitative variable as in section 2.5 will be calculated. |
| ○ Costs (i.e. out-of-pocket expenses) incurred by the caregiver that were directly related to accompanying the patient for this ERT administration episode (to include costs of travel / parking / subsistence / any other costs). | The summary statistics for quantitative variable as in section 2.5 will be calculated. |

<table>
<tr><td colspan="2">Secondary objective 3<br><br>To describe patient-reported HRQoL (measured by the SF-12), wellbeing (measured by the WHO-5), levels of fatigue (measured by the bespoke Fatigue Likert scale) and work productivity (measured by the WPAI) in patients with FD treated with ERT (with agalsidase alfa or agalsidase beta).</td></tr>
<tr><td>Summary measures of patients':<br><br>○ HRQoL (SF-12 scores/ responses)<br><br>○ General wellbeing (WHO-5 scores / responses).<br><br>○ Level of fatigue (bespoke Fatigue Likert scale).<br><br>○ Levels of work impairment (WPAI scores / responses)<br><br>○ For the bespoke Fatigue Likert scale, times (hours and minutes) of completion will also be recorded.</td><td>Questionnaire scores and/or item responses will be reported using summary statistics, as appropriate to the questionnaire and in accordance with the licensed scoring manual / instructions for use.<br><br>For these scores, the total of all items in each of these will be summarized as per section 2.5 for quantitative variables. The frequency and percentages of responses for individual items will also be given. HRQoL and Who-5 will be given for baseline (the data collected during ERT infusion visit). Fatigue score will be given for baseline and the change scores from baseline to score collected at the same day evening of ERT infusion and 15 days after 1st infusion. WPAI scores will be given one at 1-7 days after infusion and change from this to 15 days after infusion.<br><br>The summary statistics of completion time in minutes will be calculated as per section 2.5 for quantitative variables.</td></tr>
<tr><td colspan="2">Secondary objective 4<br><br>To describe work productivity (measured by the WPAI:CG) and the strain of care provision (measured by the CSI) in caregivers of patients with FD treated with ERT.</td></tr>
<tr><td>Summary measures of caregivers':</td><td>Questionnaire scores and/or item responses will be reported using summary statistics, as appropriate to the questionnaire and in accordance with the licensed scoring manual / instructions for use.</td></tr>
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| ○ Levels of work impairment (WPAI:CG scores / responses).<br><br>○ Levels of strain of providing care for a patient with FD (CSI scores / responses). | The total scores will be summarized as per section 2.5 for quantitative variables. The individual item responses will be presented using frequency and percentages.<br><br>WPAI-CG will be summarized at 1-7 days after 1st infusion and change from this to 15 days after infusion.<br><br>CSI scores collected during ERT infusion will be summarized. |
| **Patients' demographic and clinical characteristics (all patients)** | |
| Summary measures of (at date of consent, unless specified):<br><br>○ Sex (male / female).<br><br>○ Age at consent.<br><br>○ Age at onset of first symptoms.<br><br>○ Levels of strain of providing care for a patient with FD (CSI scores / responses).<br><br>○ Duration of ERT treatment.<br><br>○ ERT start date.<br><br>○ ERT treatment under observation (agalsidase alfa / agalsidase beta).<br><br>○ Number of ERT infusions received in the year prior to date of enrolment, by type | Frequency distribution with percentages will be given.<br><br>Mean age with standard deviation along with other summary measures for quantitative variables as in section 2.5 will be calculated.<br><br>The total scores will be summarized as per section 2.5 for quantitative variables. The individual item responses will be presented using frequency and percentages.<br><br>The difference between ERT start date and end date will be calculated. The summary statistics for duration of ERT treatment will be given as per in section 2.5 for quantitative variables.<br><br>The number and percentage for the number of treatments for each type of treatment will be calculated as per section 2.5.<br><br>The frequency and percentages will be provided for each type of prior history. |

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| of treatment (agalsidase alfa, agalsidase beta).<br>○ FD phenotype (organ involvement/complications), to include any current or prior history.<br>○ eGFR at enrolment (closest measurement prior and preferably within 12 months); date and measurement.<br>○ Urine protein levels at enrolment (closest measurement prior); date and measurement.<br>○ WBC alpha-galactosidase (closest prior to enrolment); date and measurement<br>○ LVMi at enrolment (closest measurement prior and preferably within 12 months); date and measurement.<br>○ FD mutation (name of mutation, if known, including: e.g. A143T)<br>○ Severity of FD (mild / moderate / severe)<br>○ Do any other relatives with whom the patient lives have FD (Yes / No / Not known). | Summary statistics for quantitative variables as described in section 2.5 will be provided for these variables.<br><br>Frequency distribution along with its percentages will be calculated for these variables. |

## 3. ANALYSIS IMPLEMENTATION

### 3.1 Interim Analysis

There are currently no plans for an interim analysis.

### 3.2 Analysis checks

Analysis of the primary endpoint, the total time spent by HCPs in the preparation and administration of a single dose of ERT in patients with FD, will be independently reviewed by a member of the Data Analysis team at Open Health who was not involved in the analysis of the final study data. No additional analysis checks will be carried out.

It is anticipated that study results will be presented to investigators to enable a preliminary discussion of the results of the study, at a meeting to be planned after completion of the data analysis and before the study report is prepared.

## 4. APPENDIX

Shell tables TBC