Clinical Investigation Plan Number: AHE-01

A Multi-Centre, Double Blind, Randomised Controlled Clinical Investigation to Validate the EPS1 Device as a Treatment for Dysphagia After Brain Injury. A Study of Swallowing Treatment Using Electrical Pharyngeal Stimulation (STEPS Study)

Statistical Analysis Plan

Quantics Consulting Limited

Version 1.3

21 March 2012
Author:
Sam Dumble MSc
Statistician
Quantics Consulting Limited
Roslin BioCentre
Edinburgh EH25 9TT

Reviewed by:
Ann Yellowlees PhD
Director
Quantics Consulting Limited
Roslin BioCentre
Edinburgh EH25 9TT

Approved by:
Joanna Love
Clinical Research Manager
Phagenesis Limited
Unit 18, Enterprise House
Manchester Science Park
Manchester M15 6SE

Approved by:
Philip Bach
Chief Investigator
Division of Stroke
University of Nottingham
City Hospital campus
Nottingham NG5 1PB
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse Device Effect</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of covariance</td>
</tr>
<tr>
<td>BI</td>
<td>Barthel Index. General capability assessment</td>
</tr>
<tr>
<td>CIP</td>
<td>Clinical Investigation Plan (may also be referred to as a protocol)</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form (may be in paper or electronic format)</td>
</tr>
<tr>
<td>DSRS</td>
<td>Dysphagia Severity Rating Scale (a validated scoring system to rate the severity of dysphagia in patients)</td>
</tr>
<tr>
<td>EPSI</td>
<td>The investigational device name for the purposes of this clinical investigation. This will not be the brand name.</td>
</tr>
<tr>
<td>EQ5D</td>
<td>A standardised instrument for use as a measure of health outcome.</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat</td>
</tr>
<tr>
<td>HCP</td>
<td>Health Care Professional</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last Observation Carried Forward</td>
</tr>
<tr>
<td>mRs</td>
<td>Modified Rankin Scale. Measurement of general ability</td>
</tr>
<tr>
<td>NG</td>
<td>Nasogastric feeding tube</td>
</tr>
<tr>
<td>NIHSS</td>
<td>National Institute of Health Stroke Scale. Global measure of stroke severity</td>
</tr>
<tr>
<td>PAS</td>
<td>Penetration Aspiration Scale</td>
</tr>
<tr>
<td>PEG</td>
<td>Percutaneous Endoscopic Gastrostomy</td>
</tr>
<tr>
<td>PES/ESP</td>
<td>Pharyngeal Electrical Stimulation/Electrical Stimulation of Pharynx (these terms are interchangeable and refer to the method of treatment)</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>Placebo</td>
<td>For the purpose of this trial placebo refers to a sham treatment being provided, meaning that the device is being compared to current standard care. No available, accepted treatments are withheld from any of the Patients</td>
</tr>
<tr>
<td>PP</td>
<td>Per-protocol</td>
</tr>
<tr>
<td>SADE</td>
<td>Serious Adverse Device Effect</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard Error of the Mean</td>
</tr>
<tr>
<td>SALT</td>
<td>Speech And Language Therapist</td>
</tr>
<tr>
<td>TOR-BSSST</td>
<td>Toronto Bedside Swallowing Screening Test</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>UADE</td>
<td>Unanticipated Adverse Device Effect</td>
</tr>
<tr>
<td>USADE</td>
<td>Unanticipated Serious Adverse Device Effect</td>
</tr>
<tr>
<td>VFS</td>
<td>Videofluoroscopy</td>
</tr>
</tbody>
</table>
# Contents

1. **Introduction** .................................................................................................................. 6  
   1.1. Purpose of Statistical Analysis Plan ............................................................................. 6  
2. **Study Objectives** .......................................................................................................... 6  
   2.1. Primary Objective ....................................................................................................... 6  
   2.2. Secondary Objectives ................................................................................................. 6  
3. **Study Design** ................................................................................................................. 6  
   3.1. Overview .................................................................................................................... 6  
   3.2. Test Device ................................................................................................................. 7  
   3.3. Sample Size ............................................................................................................... 7  
   3.4. Randomisation ........................................................................................................... 8  
   3.5. Populations ................................................................................................................. 8  
4. **Efficacy and Safety Endpoints** ...................................................................................... 9  
   4.1. Primary Efficacy Endpoint .......................................................................................... 9  
   4.2. Secondary Efficacy Endpoints (ITT population) .................................................... 9  
   4.3. Safety Endpoints (Safety Population) ....................................................................... 10  
5. **Statistical Methods** ..................................................................................................... 10  
   5.1. Statistical Analyses ...................................................................................................... 10  
   5.2. Data Handling Procedures ....................................................................................... 14  
   5.3. Statistical Software ................................................................................................... 14  

References .......................................................................................................................... 15  

Appendix A: Study Schema .................................................................................................. 16  
Appendix B: Index of Planned Outputs .............................................................................. 17  
Appendix C: Penetration Aspiration Scale (PAS) .......................................................... 22  
Appendix D: Dysphagia Severity Rating Scale (DSRS) ................................................... 23  
Appendix E: Toronto Bedside Swallowing Screening Test (TOR-BSST) ......................... 24  
Appendix F: National Institute of Health Stroke Scale (NIHSS) ..................................... 26  
Appendix G: Modified Rankin Scale (mRs) ...................................................................... 30  
Appendix H: Barthel Index (BI) .......................................................................................... 31  
Appendix I: STEPS Research Videofluoroscopy Protocol ............................................. 32
1. Introduction

1.1. Purpose of Statistical Analysis Plan
The purpose of this statistical analysis plan is to outline the necessary statistical techniques required to evaluate the efficacy and safety parameters outlined in Clinical Investigation Plan AHE-01 [1]. This covers the statistical analyses for both the final report and up to three interim reports.

2. Study Objectives

2.1. Primary Objective
To evaluate the performance of the EPS1 device in reducing the severity of unsafe swallows when compared to placebo.

2.2. Secondary Objectives
- To evaluate safety of EPS1
- To evaluate sustainability of reversal of swallowing disability at 6 and 12 week assessments compared to placebo
- To evaluate change in severity of dysphagia post treatment compared to placebo
- To evaluate length of hospital stay compared to placebo
- To evaluate chest infection rate compared to placebo
- To evaluate mortality levels compared to placebo
- To evaluate improvement in feeding status compared to placebo
- To evaluate global stroke impact between groups at 2, 6 and 12 weeks
- To evaluate ease of use
- To evaluate patient quality of life (QoL) compared to placebo
- To investigate the relationship between personality type and functional recovery

3. Study Design

3.1. Overview
This will be a European, multi-centre, prospective, randomised controlled, two-arm, double blind clinical investigation to evaluate the safety and performance of EPS1 in the treatment of dysphagia in stroke patients.
All patients admitted to the stroke unit, rehabilitation units or general medical/neurology wards with dysphagia following acute anterior cerebral circulation or brainstem stroke that meet the initial inclusion and exclusion criteria will be consented into the clinical investigation. Patients who meet the second set of inclusion criteria (dysphagia confirmed by videofluoroscopy (VFS)) will be randomised to either active or sham (placebo) treatment arms.

Patients included in this clinical investigation will be evaluated at screening and at 2 weeks, 6 weeks and 12 weeks post treatment. A study schematic is presented in Appendix A.

The Clinical Investigation will be conducted at seven sites in the United Kingdom, three sites in Germany and two sites in France, making a total of twelve sites. The recruitment period is estimated at 6 months with anticipated clinical investigation duration of 9-12 months. Each patient's participation will last approximately 12-14 weeks.

A total of 140 patients meeting the screening and randomisation inclusion and exclusion criteria set forth will receive active or sham Electrical Pharyngeal Stimulation (EPS) using the EPS1 device.

3.2.  Test Device
The medical device is intended for professional use and is designed for the treatment of oropharyngeal dysphagia in patients post stroke. The device functions by using electrical stimulation of the pharynx to effect sensorimotor reorganisation of control of the swallowing function in the brain. Treatment will be administered once a day for three days. The process for the placebo group will be the same as those in the active group; site staff will be trained on how to administer 'sham' treatment.

3.3.  Sample Size
The primary endpoint for the study is: the change in mean penetration-aspiration scores (PAS) on the videofluoroscopy protocol, 2 weeks after randomisation. The sample size is based on the data gained from a placebo-controlled pilot study (Jayasekaeran V et al (2010) [2]).

The mean values of the change in mean PAS in the two randomised groups of sizes 16 and 12 were -1.4 and -0.1, giving an observed treatment effect of 1.3. The standard deviations in
each group were 1.9 and 1.5 respectively. The distributions of values in each group were approximately normal, with standard deviation of 1.8.

Sixty patients in each group would provide 90% power to detect a difference of approximately 1.1 in the change in mean PAS score, based on a comparison of change in mean PAS between the two groups using a 2 sided t test, with alpha = 5%. The study is expected to provide higher power than this because the primary endpoint will be adjusted for dysphagia severity at baseline.

To account for the loss of information caused by the potential for fewer than six swallows being available for every patient, and to account for patients dropping out before the two week assessment, it is recommended to increase this number by approximately 15%.

Therefore, 140 patients will be recruited.

3.4. Randomisation

The patients will be randomised in a 1:1 ratio between the treatment groups. Allocation will be by randomly permuted blocks and stratified by centre and feeding status (presence/absence of artificial feeding) to enhance balance. Stratifying by centre also ensures that balanced groups will also be achieved in each country. At each of the 12 sites, a minimum of 6 subjects will be recruited, up to a maximum of 18 subjects per site. Therefore, 72 subjects (12 x 6) will be randomised via site allocation and the remaining 68 will be allocated via competitive recruitment to meet the required sample size of 140 subjects.

3.5. Populations

3.5.1 Target population

The target population is patients with dysphagia following acute anterior cerebral circulation or brainstem stroke that meet all the inclusion and exclusion criteria and who are considered eligible to be entered into this clinical investigation.

3.5.2 Intention to treat population

The Intention to treat (ITT) population is defined as all randomised patients.
3.5.3 Safety population

The safety population is defined as any patient who received at least one administration of either treatment.

3.5.4 Per protocol population

The per protocol population is defined as any patient who received the complete course of treatment and underwent VFS at the screening assessment and at visit 4.

4. Efficacy and Safety Endpoints

4.1. Primary Efficacy Endpoint

- Change from baseline in mean PAS score at 2 week assessments. This will be calculated over all swallows – both the initial six 5ml swallows and any subsequent swallows from the 50ml cup. This is expected to be no more than ten swallows.

4.2. Secondary Efficacy Endpoints (ITT population)

- Change in mean PAS at 12 week assessment
- Toronto Bedside Swallowing Screening Test (TOR-BSST) at 2 and 12 week assessments (see Appendix F)
- Change in Dysphagia Severity Rating Scale (DSRS) at 2 and 12 week assessments (see Appendix E)
- Change in National Institute of Health Stroke Scale (NIHSS) at 2 and 12-week assessments (see Appendix G)
- Change in Modified Rankin Scale (mRS) and Barthel Index (BI) at 2, 6 and 12-week assessments (see Appendices H,I)
- Frequency of chest infection up to discharge or 12-week follow up (whichever is sooner)
- Time from randomisation to death (within 12-week follow-up)
- Time from randomisation to removal of Nasogastric (NG) feeding tube or Percutaneous Endoscopic Gastrostomy (PEG) tube in relevant sub-stratum
- Feeding status as 2, 6 and 12 weeks
- Weight at 2 and 12 week assessments
- Mid arm circumference at 2 and 12 weeks
• BMI at 2 and 12 weeks
• Albumin at 2 and 12 week assessment
• Discharge destination
• Ease of use of the device by way of questionnaire to HCPs delivering (real or sham) treatment.
• QoL by means of EQ-5D [3]
• To evaluate the relationship between personality type and functional recovery

4.3. Safety Endpoints (Safety Population)

• Incidence of all of adverse events, adverse device effects, serious adverse events, serious adverse device effects and unanticipated serious adverse device effects

5. Statistical Methods

5.1. Statistical Analyses

In all analyses a 2-sided significance level of 5% (p-value < 0.05) will be used to determine if the difference between the two treatment groups is statistically significant. All secondary endpoints are exploratory and therefore no adjustment for multiple testing will be applied.

5.1.1 Primary efficacy analysis

The primary endpoint for the study is the change in the mean PAS score between screening and two week assessment. Analysis will be carried out using an unadjusted Student’s t-test and also an analysis of covariance (ANCOVA) model adjusted for the stratification variables (site and feeding status) and other key indicators (baseline mean PAS, baseline NIHSS and age) to determine if there is a statistically significant difference between the active treatment group and the sham treatment group.

This analysis will be carried out on a number of different populations to ensure robustness in the results:
• All randomised patients (ITT population)
• All patients receiving any treatment session (sham or active) (Safety population)
• All patients receiving all three treatment sessions
• All patients undergoing VFS at two weeks
• All patients undergoing VFS at two weeks and receiving any treatment session
• All patients undergoing VFS at two weeks and receiving all three treatment sessions
  (per protocol population)

Analyses will only be carried out on all of these populations where they do not completely overlap with a previously analysed population.

5.1.2 Secondary efficacy analysis

The following endpoints will be analysed using repeated measures analysis of covariance models to investigate the treatment effects:

• Change in mean PAS (at 12 weeks)
• Change in DSRS

The ANCOVA model will fit an autoregressive first order variance covariance structure (AR (1)), to model the relationship over time (visits) of the endpoint of interest as the dependent variable (change in mean PAS or change in DSRS).

The ANCOVA model will include the following parameters as factors and covariates:
Factors: Treatment, feeding status, visit
Covariates: Baseline value of dependent variable

Centre will be fitted as a random effect and the interaction between treatment and visit will also be fitted.

Adjusted mean values and 95% confidence intervals will be tabulated and plotted for the results at baseline and the 2 week and 12 week assessments. P-values will also be calculated from the models to determine the significance of each of the factors upon the dependent variable.

For the following continuous endpoints the Mann Whitney U test or Student’s t-test will be used as appropriate. In order to test if the underlying assumptions of normality required for Student’s t-test are valid the Shapiro-Wilk test will be performed. If the Shapiro-Wilk test
indicates that there are significant violations of underlying normality (p-value < 0.05) the Mann-Whitney U test will be used.

- Change in mean PAS at 12 weeks after randomisation
- Change in DSRS score at 2 and 12 week assessments - see Appendix D
- Change in NIHSS scores at 2 and 12-week assessments – see Appendix F
- Change in mRs scores at 2, 6 and 12-week assessments – see Appendix G
- Change in BI scores at 2, 6 and 12-week assessments – see Appendix H
- Change in weight (kg) at 2 and 12 week assessments
- Change in mid arm circumference (cm) at 2 and 12 weeks
- Change in albumin (g/dL) at 2 and 12 week assessment
- Change in BMI (kg/m\(^2\)) at 2 and 12 week assessment

Survival analysis will be performed for the following endpoints:
- Time from randomisation to death (days)
- Time from randomisation to removal of NG or PEG tube (days) for patients with artificial feeding status at screening
- Time from randomisation to discharge from hospital (days).

A Kaplan-Meier plot for each survival analysis will be produced showing the survival functions of the two treatment groups. Incidence percentage, percentage censored, median survival time and hazard ratios (and their 95% confidence intervals) will be calculated for the two treatment groups. A Log-Rank test will be used to determine if the difference in survival between the two treatment groups is statistically significant. The analysis will be restricted to the 12 weeks of the study and censoring will occur if a patient withdrew from the study before experiencing the endpoint in question.

The following secondary endpoints will be tabulated and compared between the two treatment groups using Fisher’s exact test:
- TOR-BSST at 2 and 12 weeks.
- All PAS≤3 (patient has no dysphagia) at 2 and 12 weeks
- Feeding status (artificial or non-artificial) at 2, 6 and 12 weeks.
- Incidence of chest infection up to discharge or 12 week follow up

Discharge destination will be compared between groups using Pearson’s chi-squared test.
Ease of use of the device and QoL at 12 week assessment from EQ-5D [3] will also be summarised.

The analysis investigating the relationship between personality type and functional recovery will be carried out independently of the other analyses and will not be performed by Quantics.

5.1.3 Safety analysis

The numbers and percentages of patients experiencing any adverse event (AE), any adverse device effect (ADE), any serious adverse event (SAE), any serious adverse device effect (SADE), and any unanticipated serious adverse device effect (USADE) will be summarised per treatment group. The numbers and percentages of patients experiencing any adverse events will also be summarised by maximum severity and relatedness to study treatment per treatment group.

AEs will be summarised by system organ class and preferred term, by relatedness to study treatment and by severity, per treatment group. ADEs will be summarised by preferred term and severity per treatment group. All AEs, ADEs, SAEs and SADEs and USADEs for each patient will also be listed.

Concomitant medications taken by more than 2% of the total patients and the number of patients taking medication in each ATC level 2 group will be summarised by treatment group.

5.1.4 Additional summaries

All demographic and baseline characteristics captured in the CRF will be summarised by treatment group and across the whole trial. For both continuous variables (e.g. age) and ordinal variables (e.g. DSRS) descriptive statistics will be presented (mean, standard deviation, median, minimum, maximum, interquartile range and number of participants with data). For categorical variables (e.g. sex) frequencies, percentages and number of participants with data will be presented. The denominator for the percentages will be the number of patients with non-missing data.
Summaries will include the following:

- Patient disposition (i.e. number of patients completing each visit) across all study visits, and reasons for withdrawal
- Patient demography (e.g. age, sex, etc.)
- Baseline stroke characteristics (e.g. stroke classification, side of stroke, etc.)
- Treatment dose information

5.1.5 Listings

All data captured in the study will be listed. This will include outcomes not included in summaries such as concomitant medication, medical history and pregnancy status.

5.2. Data Handling Procedures

5.2.1 Missing data

For the primary analysis if the VFS is stopped before the final swallow then the average PAS score will be calculated from the completed swallows.

In the case of analysis carried out using survival methods patients will be included for all time points where data is non-missing and will be censored from the last known result onwards.

For all other analyses missing data will be excluded from the analyses and the number of patients with missing results will be summarised.

5.2.2 Rounding

All results will be presented to two decimal places or an appropriate number of significant figures for the magnitude of the results.

5.3. Statistical Software

Data manipulation, statistical summaries and statistical analyses will be performed using SAS® version 9.3 or higher on Windows [4]. Some analysis may be carried out in R version 2.14.0 or higher [5]. All statistical outputs will be validated independently by another statistician.
References


