TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	An Exploratory Study to Investigate the Use of Biotelemetry to Identify Markers of Disease Progression in Subjects with Amyotrophic Lateral Sclerosis

Compound Number: Non-compound specific

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Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2014N211002_00	2014-DEC-12	Original
2014N211002_01	2015-APR-09	Amendment No. 1
The purpose of this amendment is to: 1) clarify bullet 5 in Exclusion Criterion #3; 2) add a requirement to enter into the eCRF, concomitant medications and non-drug therapies used to treat AEs\SAEs as defined in the protocol; 3) add hyperreflexia to the neurological examinations; 4) and to make other minor clarifications to the text.		
2014N211002_02	2015-SEP-21	Amendment No. 2
The purpose of this amendment is to: 1) modify the age requirement from 50 to 75 years to 18 to 80 years (Inclusion Criterion #1); 2) modify the time frame in Inclusion Criterion #3 from 12 months to 18 months between symptom onset and ALS diagnosis (and amend the description of the population accordingly); 3) clarify bullet 4 in Exclusion Criterion #3, 4) clarify that muscle atrophy is one of the limb symptoms to be included as part of the neurological examination, , 5) to make other minor clarifications to the text.		

SPONSOR SIGNATORY

PPD

21/09/2015

Marina Zvartau-Hind MD, PhD Date

VP Head of Clinical Development

R&D Neurosciences Therapy Area Unit

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Medical Monitor	PPD MD, PhD	PPD	PPD	PPD	GlaxoSmithKline Research and Development Limited Iron Bridge Road Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
SAE contact information	Case Management Group, GCSP	PPD		PPD	

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): None

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 201283

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 201283

Rationale

This study is being conducted as the first step for developing new meaningful measure(s) which might prove to be more effective than existing measures for monitoring clinical function and disease course in amyotrophic lateral sclerosis (ALS). The objective of this study is to test novel measures of movement/physical activity, heart rate and speech and explore how they measure disease progression by evaluating their relationship to gold standard measures of function. The ultimate aim of this research is to identify and develop sensitive, real-time measures of ALS disease progression which might have utility as clinically meaningful endpoints in future ALS studies.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Exploratory	
Explore the application of actigraphy: • For measuring movement/physical activity in ALS subjects • As a marker of ALS disease progression	• Change over time in measurements of movement/physical activity by accelerometer. • Relationship between the ALS Functional Rating Scale - Revised (ALSFRS-R) and accelerometer measures of movement/activity. • Validate the movement/physical activity algorithms against in-clinic reference tasks of movement to ensure the algorithms are correctly capturing the defined activity.
Explore the application of continuous remote-monitoring of heart rate measures: • For measuring autonomic nervous system function in ALS subjects • As a marker of ALS disease progression	• Change over time in heart rate variability (HRV) as measured by a heartbeat sensing electrode. • Relationship between the ALSFRS and biotelemetry measures of HRV.
Explore the application of digital, quantitative speech testing: • For measuring speech quality in ALS subjects • As a marker of ALS disease progression.	• Change over time in digital speech measures of vowel, running speech and word measurements as captured by a high fidelity, acoustic sound capture interface. • Relationship between the ALSFRS and digital measures of speech. • Relationship between Forced Vital Capacity (FVC) and digital measures of speech.

Objectives	Endpoints
Explore the impact of the accelerometer and electrode devices on everyday life in subjects with ALS	Subject/caregiver feedback.
Explore the feasibility of biotelemetry transmission of movement/physical activity and HRV data.	Assessed by successful data transmission from the telecommunications hub (LifeInsight) to the central secure server at McLaren Applied Technologies (MAT).
Safety	
Monitor safety and tolerability.	Type and incidence of adverse events (AEs) secondary to the devices used in this study or due to study procedures.

Overall Design

Study 201283 is an exploratory, non-controlled, non-drug study in ALS patients. The study consists of two phases:

1. A variable length Pilot Phase to test and confirm the algorithms are capturing movement/physical activity, ensure the data transfer device is working correctly, and understand the reliability and ease of use/acceptance of the accelerometer and electrode. Subjects will attend at least 1 clinic visit to perform a series of set reference tasks while wearing the accelerometer and electrode. Subjects will also continuously wear the accelerometer and electrode in their routine home-life setting for approximately 3 days after the clinic visit (i.e., home monitoring). Repeat clinic visits and home monitoring might be necessary if data indicate the algorithms or equipment are not performing as expected. It is estimated that 5 subjects will participate in this Pilot Phase; however, the number may be less or more depending on the data generated. Subjects in the Pilot Phase will continue in the study and participate in the Core Study Phase.

2. A 48 week Core Study Phase to evaluate how measures of movement/physical activity, speech and HRV relate to ALS disease progression. During this phase, subjects will attend 5 clinic visits to perform gold standard measures of function and perform a series of set reference tasks while wearing the accelerometer and electrode. Subjects will also continuously wear the accelerometer and electrode in their routine home-life setting for approximately 3 days after the clinic visits (i.e., home monitoring). In between clinic visits, subjects will attach the accelerometer and electrode and wear it for approximately 3 days in their home. A telephone contact with the subject will be made by the site at the end of each 3-day home monitoring period.

Data will be reviewed in-stream by GlaxoSmithKline (GSK) and McLaren Applied Technologies (MAT) throughout the Pilot and Core Study Phases to understand the utility of the measures and algorithms, the functionality of the data transmission process, and the durability and ease of use/acceptance of the selected accelerometer and electrode. Generated data may result in modifications to the study, such as: changes to the devices/equipment; repositioning of the accelerometer/electrode; modification to the

algorithms, the supportive data collection plan or the data transmission process; dropping measures/tests which are not achievable. The output is therefore not prescriptive. Progression from the Pilot Phase to the Core Study Phase will be based on thorough review of the generated data. The Core Study Phase will only progress once the data from the Pilot Phase is fully interrogated.

Type and Number of Subjects

Male and female subjects 18 to 80 years of age with ALS will be enrolled into the study. Treatment of enrolled subjects will be consistent with local standard of clinical care for ALS patients. A maximum of 25 subjects will be enrolled such that approximately 20 subjects complete the study with 48 weeks of data.

Analysis

The study is designed to explore if there is a relationship between change from baseline in the physical activity/movement, heart rate and speech endpoints and change from baseline in the gold standard measures of function (ALSFRS-R and FVC). The analyses are all exploratory. Correlation between change from baseline in the movement/physical activity, heart rate and speech measures and change from baseline in the ALSFRS-R or FVC (as appropriate) will be explored. Depending on the strength of correlation between the endpoints further analyses may be performed.

2. INTRODUCTION

2.1. Background and Study Rationale

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease that affects motor neurons and is characterized by progressive weakness leading to impaired speech, swallowing, mobility and respiration. The average survival time for ALS is 2-3 years from symptom onset [Talbot, 2009]. Riluzole is the only licensed medicine which affects the ALS disease course and it has only a modest effect on survival. Thus, there remains a significant unmet medical need in ALS for therapies to slow progression of functional decline and improve survival.

Numerous therapies and experimental agents have been tested in ALS and have failed, suggesting a potential need to improve measures of disease progression and overall study design. Existing measures have limitations in terms of sensitivity hence requiring long trials with large sample sizes. The gold standard measure of function, the ALS Functional Rating Scale - Revised (ALSFRS-R), relies on subject perception of their function versus direct assessment of function. Testing burden in trials is heavy and involves a number of assessments for overall function, respiratory function, and muscle strength; this can be tiring for subjects particularly as the disease progresses leading to subject drop out and missing data such that ability to draw conclusions from the data is impacted.

Measures which could more objectively and sensitively detect a clinically meaningful change in function and disease progression might enable smaller trials, thus reducing the need for such large trials in this rare population. An endpoint which could assess clinically meaningful functional change in a more 'holistic' manner might reduce the need for multiple tests thus alleviating patient burden and missing data. Real-time measurement of function might allow for quicker interrogation of data and shorter trials thus delivering medicines in this life threatening disease faster.

This study is being conducted as the first step for developing new meaningful measure(s) which might prove to be more effective than existing measures for monitoring clinical function and disease course in ALS. The objective of this study is to test novel measures of movement/physical activity, heart rate and speech and explore how they measure disease progression by evaluating their relationship to gold standard measures of function. The ultimate aim of this research is to identify and develop sensitive, real-time measures of ALS disease progression which might have utility as clinically meaningful endpoints in future ALS studies.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Exploratory	
Explore the application of actigraphy: • For measuring movement/physical activity in ALS subjects • As a marker of ALS disease progression	• Change over time in measurements of movement/physical activity by accelerometer. Measurements may include but not be limited to: total time spent walking, time spent sitting, time spent standing, time spent active, time spent sedentary, average duration of walking periods, number of continuous walking periods >5mins, time spent walking on stairs, Total Activity Score (amount and intensity of movement), Sleep Fragmentation Index. • Relationship between the ALSFRS and accelerometer measures of movement/activity. • Validate the movement/physical activity algorithms against in-clinic reference tasks of movement to ensure the algorithms are correctly capturing the defined activity. Reference tasks may include but are not limited to: sitting, standing, sit to stand, stand to sit, walking, climbing stairs, lying, stand to lying, lying to stand and dexterity.
Explore the application of continuous remote-monitoring of heart rate measures: • For measuring autonomic nervous system function in ALS subjects • As a marker of ALS disease progression	• Change over time in heart rate variability (HRV) as measured by a heartbeat sensing electrode. Measurements may include but not be limited to: HRV standard deviation over 5mins, HRV low frequency/high frequency (LF/HR) variation over 5mins, Sleep Fragmentation Index. • Relationship between the ALSFRS and biotelemetry measures of HRV.
Explore the application of digital, quantitative speech testing: • For measuring speech quality in ALS subjects • As a marker of ALS disease progression.	• Change over time in digital speech measures of vowel, running speech and word measurements as captured by a high fidelity, acoustic sound capture interface. Measurements may include but not be limited to: central tendency of fundamental frequency, jitter, shimmer,

Objectives	Endpoints
	maximum gap between words, speaking rate, average phoneme rate, and maximum phonation time. • Relationship between the ALSFRS and digital measures of speech. • Relationship between Forced Vital Capacity (FVC) and digital measures of speech.
Explore the impact of the accelerometer and electrode devices on everyday life in subjects with ALS	Subject/caregiver feedback. Feedback may include but not be limited to: comfort of the devices, ease of applying the devices, and ease of data transmission process.
Explore the feasibility of biotelemetry transmission of movement/physical activity and HRV data.	Assessed by successful data transmission from the telecommunications hub (LifeInsight) to the central secure server at McLaren Applied Technologies (MAT).
Safety	
Monitor safety and tolerability.	• Type and incidence of adverse events (AEs) secondary to the devices used in this study. • Type and incidence of AEs due to study procedures.

4. STUDY DESIGN

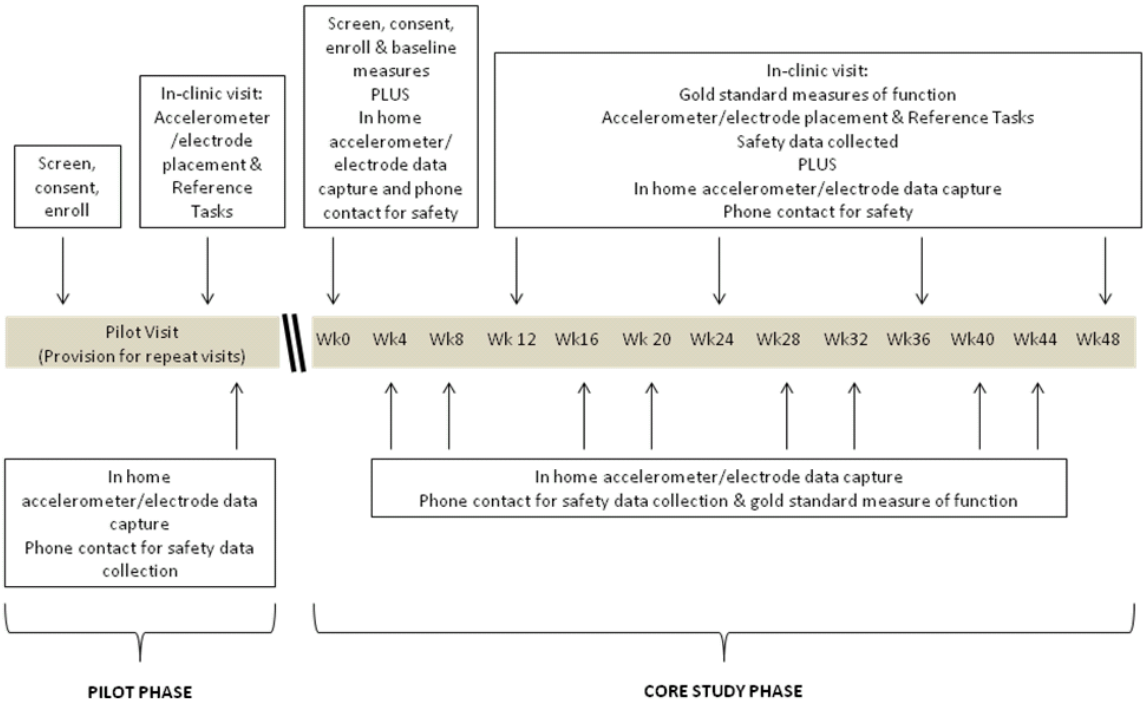
4.1. Overall Design

Study 201283 is an exploratory, non-controlled, non-drug study in ALS patients. The study consists of two phases:

1. A variable length Pilot Phase to test and confirm the algorithms are capturing movement/physical activity, ensure the data transfer device is working correctly, and understand the reliability and ease of use/acceptance of the accelerometer and electrode. Subjects will attend at least 1 clinic visit to perform a series of set reference tasks while wearing the accelerometer and electrode. Subjects will also continuously wear the accelerometer and electrode in their routine home-life setting for approximately 3 days after the clinic visit (i.e., home monitoring). Repeat clinic visits and home monitoring might be necessary if data indicate the algorithms or equipment are not performing as expected. See Figure 1. It is estimated that 5 subjects will participate in this Pilot Phase; however, the number may be less or more depending on the data generated. Subjects in the Pilot Phase will continue in the study and participate in the Core Study Phase.

2. A 48 week Core Study Phase to evaluate how measures of movement/physical activity, speech and HRV relate to ALS disease progression. During this phase, subjects will attend 5 clinic visits to perform gold standard measures of function and perform a series of set reference tasks while wearing the accelerometer and electrode. Subjects will also continuously wear the accelerometer and electrode in their routine home-life setting for approximately 3 days after the clinic visits (i.e., home monitoring). In between clinic visits, subjects will attach the accelerometer and electrode and wear it for approximately 3 days in their home. A telephone contact with the subject will be made by the site at the end of each 3-day home monitoring period. See Figure 1.

Figure 1 Study Schematic



Data will be reviewed in-stream by GlaxoSmithkline (GSK) and McLaren Applied Technologies (MAT) throughout the Pilot and Core Study Phases to understand the utility of the measures and algorithms, the functionality of the data transmission process, and the durability and ease of use/acceptance of the selected accelerometer and electrode. Generated data may result in modifications to the study, such as: changes to the devices/equipment; repositioning of the accelerometer/electrode; modification to the algorithms, the supportive data collection plan or the data transmission process; dropping measures/tests which are not achievable. The output is therefore not prescriptive. Progression from the Pilot Phase to the Core Study Phase will be based on thorough review of the generated data. The Core Study Phase will only progress once the data from the Pilot Phase is fully interrogated.

4.2. Type and Number of Subjects

Male and female subjects 18 to 80 years of age with ALS will be enrolled into the study. Treatment of enrolled subjects will be consistent with local standard of clinical care for ALS patients. A maximum of 25 subjects will be enrolled such that approximately 20 subjects complete the study with 48 weeks of data.

4.3. Design Justification

4.3.1. General Design

Application of actigraphy measures of movement/physical activity, measures of heart rate and quantitative measures of speech for real-time measurement of function and disease progression in ALS is highly novel; therefore, a stepwise approach to the study design has been undertaken. The study consists of two phases, a variable length Pilot Phase and a 48 week Core Study Phase. A two phase approach is being utilized to allow for refinement of the algorithms, equipment and data transmission processes during the Pilot Phase and enable adaptation of components which may not be fit for purpose or working well before embarking on the Core Study Phase where measures of movement, heart rate and speech will be evaluated as possible measures of disease progression. In such an exploratory setting, the two part design helps mitigate taking forward equipment, algorithms, data capture methods and data transmission processes that may require adaptation and lessens the risk that major changes will be needed during the Core Study Phase.

4.3.2. Population

The chosen population for study is a subset of the overall ALS population and consists of ALS subjects that have mild to moderate disease and have a relatively high level of clinical function at baseline. The selected population is expected to experience a functional decline during the 48 week study period of approximately 1 ALSFRS-R point /month (See Section 8.2.1). This level of decline represents typical natural history of the disease and is thought to be sufficient to start to understand the relationship between gold standard measures of clinical function and the novel measures of movement/physical activity, speech and HRV.

4.3.3. Choice of Endpoints

4.3.3.1. Movement/physical activity

ALS results in progressive wasting and paralysis of voluntary muscles leading to an inability to move one's arms, legs and body [Talbot, 2009; Kiernan, 2011]. A measurement of movement/physical activity could be a meaningful endpoint for monitoring ALS disease progression.

Daily activity and walking can be measured over time using motion-sensing devices, such as accelerometers, which measure positional change and motion. Walking behaviour, sedentary behaviour, and postural transitions as measured by an accelerometer have been shown to provide a composite picture of daily activity in healthy elderly

subjects [Lord, 2011]. To date, accelerometer data have not been reported for ALS patients; however, accelerometers have been shown to have utility across other neurological conditions with mobility problems. Post stroke actigraphy has been shown to be a useful tool to measure recovery of function [Reiterer, 2008], monitor general patterns and amount of activity [Craig, 2012; Gebruers, 2010; Lindemann, 2012], and has been shown to correlate with clinical scales [Gebruers, 2010]. In Parkinson's Disease, actigraphy has been shown to effectively monitor ambulatory activity [Lord, 2013] and activity data has been shown to correlate with clinical scales [Pan, 2013]. Wireless accelerometer applications have also successfully quantified and monitored hand tremor in Parkinson's disease [LeMoyne, 2010; LeMoyne, 2013].

4.3.3.2. Heart Rate Variability (HRV)

Autonomic function is known to be impaired in ALS [Pavlovic, 2010; Merico, 2011; Pinto, 2012]. HRV is a measure of autonomic function and analysis of HRV may prove useful in early detection of autonomic nervous system abnormalities, including sympathetic hyperactivity and sympathovagal imbalance [Shimizu, 2013]. In particular, increase in low frequency/high frequency (LF/HF) ratio has been reported to be linked with the imbalance of sympathovagal function [Pisano, 1995], while decreased LF and HF bands with reduced baroreflex sensitivity and diminished cardiorespiratory transfer has been reported during normal breathing in ALS [Linden, 1998]. Additionally, reduced HRV has been identified as a potential mortality risk factor in ALS [Pinto, 2012]. Therefore, continuous real-time measurement of HRV could be a meaningful endpoint in ALS.

4.3.3.3. Speech

Speech is produced as a result of muscle and respiratory function [Green, 2013], which are both affected in ALS. ALS results in progressive bulbar motor deterioration leading to impaired speech and swallowing and complications from these bulbar symptoms can significantly impact survival [Green, 2013]. Pseudobulbar manifestations may also contribute to speech impairment. Speech measurement is part of the assessment of bulbar function in ALS; however, many of the available tests do not provide meaningful information on disease progression [Green, 2013]; therefore, an easy to use, quantitative measure of speech might be a meaningful endpoint for monitoring ASL disease progression.

4.3.3.4. ALSFRS-R and FVC

ALSFRS-R is a gold standard measure of functional decline in ALS and is routinely used to monitor disease progression and evaluate treatment effects in clinical trials and in clinical practice [Brinkmann, 1997; Cudkowicz, 2004; Cedarbaum, 1999]. In order for any new outcome measure to be clinically meaningful and relevant to physicians and regulators, it will need to correlate to the ALSFRS-R.

FVC is considered a gold standard measure of respiratory function in ALS and is routinely used to monitor disease progression and evaluate treatment effects in clinical trials [Brinkmann, 1997; Cudkowicz, 2004]. FVC, as a measure of lung capacity, may

help explain the physical effects of air flow over the glottis and the impact of reduced respiratory function on phonation and speech.

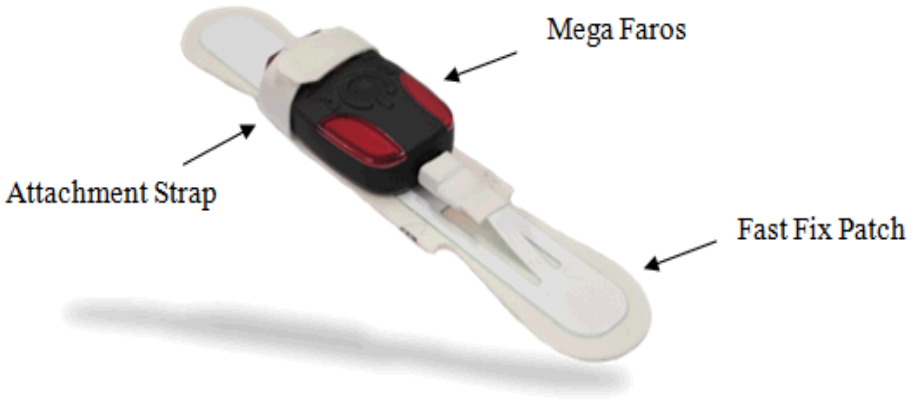
4.3.4. Choice of Devices

4.3.4.1. Medical Devices: Accelerometer and Heartbeat Sensing Electrode

The selected accelerometer is the commercially available eMotion Faros 180° ECG Sensor manufactured by Mega. The selected heartbeat sensing electrode is the commercially available Fast Fix electrode patch manufactured by Mega. Both devices are CE-marked under the Medical Device Directive 93/42/EEC.

The Faros sensor is a wearable, externally applied, accelerometer and electrocardiograph recorder and transmitter that is intended for health monitoring and scientific research in both clinical and non-clinical settings; it does not have any analysis or diagnostic capability [Mega Electronics Ltd, 2014]. The Faros sensor measures physical activity and has the capacity to record heart rate variability. Physical activity is captured via the 3-axis accelerometer within the Faros sensor. Heart rate is captured via electrodes in the Fast Fix electrode patch and transmitted to the Faros sensor via a Universal Serial Bus (USB) connection. The Fast Fix electrode patch also has adhesive strips which secure the Faros sensor and Fast Fix electrodes together. See Figure 2. The physical activity and heart rate data are transmitted from the Faros sensor to the data transmission system via secure Bluetooth wireless signal.

Figure 2 Mega Faros Sensor



The advantages for using the Faros sensor and Fast Fix electrode patch are:

- Ability to collect both physical activity data and heart rate data.
- Ability to buffer and store a subject's data for the duration of the study which prevents data loss.
- Ability to transmit the physical activity and heart rate data via Bluetooth which prevents having to manually download data and allows for in-stream data transmission and review of data by GSK and MAT which facilitates in-stream decision making and informed adaptations.

4.3.4.2. Data Transmission Device: LifeInsight Hub

The LifeInsight hub was developed by MAT as a platform to enable easy, real-time transmission of data for research purposes (see Figure 3). The hub is CE-marked under the Radio and Telecommunications Terminal Equipment Directive 1999/5/EC.

Figure 3 LifeInsight Hub

The hub receives data from the accelerometer via secure Bluetooth wireless signal every 2mins. The hub then automatically uploads the data in real-time (every 10 minutes) to secure servers at MAT via a secure connection on the 3G mobile phone network. The hub also has sufficient memory to retain a copy of all data generated for a subject at a site for the duration of the trial. This system of biotelemetry data transmission has several advantages, specifically the hub:

- Enables real-time monitoring of data at GSK/MAT which facilitates in-stream decision making and informed adaptations for the study.
- Ensures data is transmitted in-stream to MAT which minimizes the impact of lost hubs or accelerometers.
- Ensures a copy of the data is securely retained so that data will not irrevocably be lost during the transmission/upload process.
- Prevents having to download data from the accelerometer and upload the data to the secure server via a manual process.
- Avoids issues associated with installing software on local computers in hospitals/clinics.
- Avoids issues with local firewalls for data transmission/upload to secure servers.

4.4. Benefit:Risk Assessment

The following section outlines the risk assessment and mitigation strategy for this protocol as well as the potential benefit to subjects.

4.4.1. Risk Assessment

Potential Risk of Clinical Significance	**Management/Mitigation**
Trial Risks	
Subjects may consider the nature and extent of the assessments to be a burden and prohibitive for enrolment or continuation in the study.	The protocol has been designed to follow the standard in-clinic visit schedule for ALS treatment and monitoring and the selected measures of function are familiar to ALS patients and are part of routine disease monitoring. In-stream feedback will be obtained on the ease of use/acceptance of the devices. Every attempt will be made to incorporate the feedback to reduce subject/caregiver burden.
There is negligible risk for pregnant females and women of childbearing potential (WCBP) to wear or handle the devices in this study.	The nature and intensity of the wireless signals used to transmit the data are equivalent to a mobile phone or less.
Medical Device Risks	
The medical-grade hypoallergenic adhesive used to attach the devices might result in a local skin allergic reaction such as: irritation, inflammation or itching.	Subjects with a known hypersensitivity to adhesives are excluded from the study. Subjects are informed of this potential risk in the Informed Consent Form (ICF). Subjects are instructed to remove the devices if a reaction occurs and contact the site for further instructions. Adverse events (AEs) and serious adverse events (SAEs) considered attributable to the medical devices will be reported. Subjects are provided with instructions on proper use of the device.
Because the sensor uses Bluetooth wireless signal to transmit data, there is a risk of electromagnetic interference with other medical devices.	Subjects with an active implantable cardiac medical device (e.g. pacemaker or implantable cardioverter-defibrillator) are excluded from the study. Subjects at high risk for requiring external defibrillation are excluded from the study. Subjects are advised to notify the site prior to any medical or surgical procedure. Subjects are provided with instructions on proper use of the device.
Dismantling or submerging the sensor in water might result in electrical shock	The sensor does not have any electrical stimulation capabilities and has not been shown to cause electrical shock in case of accidental water contact in healthy volunteers. Subjects are provided with instructions on proper handling of the device. AEs and SAEs considered attributable to the medical devices will be reported.
Extreme humidity or temperature might result in device malfunction.	Subjects are provided with instructions on proper care of the device.

Potential Risk of Clinical Significance	**Management/Mitigation**
Data Transmission Device Risks	
Non-secure data transfer could result in disclosure of unintended personally identifiable information (PII).	The data transmitted through the hub does not contain PII. Subject information and data security will be handled according to GSK Standard Operating Procedures and policies.
The data transfer process from sensor to hub and hub to MAT might result in missing data or inaccurate data.	The Bluetooth pairing between the sensor and the hub is locked to prevent unintended pairing to other Bluetooth-enabling devices. Each subject is assigned a specific sensor and hub; the data from the subject will be identified by the combination of the unique serial numbers on the sensor and hub. The hub has memory capacity to store data for the duration of the trial. The hub automatically uploads data to MAT in stream.
Dismantling or submerging the hub in water might result in electrical shock.	Subjects are provided with instructions on proper care of the hub. AEs and SAEs considered attributable to the data transmission device (hub) will be reported.

4.4.2. Benefit Assessment

Subjects will not have direct clinical benefit from participating in this study. Subjects will continue their usual standard of care as prescribed by their healthcare provider and will continue to follow up with their regular physician for their ALS healthcare during the study. Subject participation will contribute to the overall knowledge of disease progression measurement in ALS, which may have utility in future clinical investigations.

4.4.3. Overall Benefit: Risk Conclusion

The available data package for the devices used in this study establishes reasonable assurance the devices are safe for their intended use in the trial when utilized in accordance with instructions for use. The risks to subject safety have been mitigated and controlled based on subject eligibility criteria, subject instructions, device labelling, and testing certifications of the CE-marked devices supplied in the study. The overall risk to subjects is therefore considered to be minimal. While there is no individual subject benefit, the development of potentially better and more effective measures for monitoring disease progression might provide benefit for future ALS clinical trials, and may advance understanding of ALS and development of future treatments.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. Between 18 and 80 years of age, inclusive, at the time of signing the informed consent.
TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Diagnosed with ALS by a neurologist with expertise in ALS. For subjects with bulbar onset there must be objective limb involvement of at least one limb. 3. Diagnosed with ALS within 18 months of symptom onset. 4. Subjects must be ambulatory (i.e., must not be confined to a wheelchair).
SEX
5. Male and female subjects.
INFORMED CONSENT
6. Capable of giving signed (or verbal consent or assent where applicable) informed consent as described in Section 9.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.
OTHER
7. Capable and willing to comply with the requirements of the protocol (either by themselves or with assistance).

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. Neurological (other than the subject's ALS) or non-neurological co-morbidities (e.g. joint disease, respiratory disease) which limit mobility. 2. Clinically significant cognitive impairment in the opinion of the investigator. 3. Regionally restricted forms of ALS, or other atypical variants: • Isolated corticobulbar pattern of ALS with normal ambulation • Flail arm syndrome • Primary lateral sclerosis • Signs of chronic partial denervation restricted to a single limb • ALS parkinsonism dementia complex 4. Subjects requiring mechanical ventilation (non-invasive ventilation for sleep apnoea is allowed). 5. Historical or current evidence of clinically significant uncontrolled disease which, in the opinion of the investigator, would put the safety of the subject at risk through participation or impact the study assessments or endpoints.
OTHER CRITERIA
6. Presence of an active implantable cardiac medical device (*e.g.*, pacemaker or implantable cardioverter-defibrillator) or at a high risk for needing external defibrillation. 7. History of skin hypersensitivity to adhesives. 8. Current participation in a clinical trial which in the opinion of the investigator and GSK medical monitor might impact the objectives of this study.

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently enrolled. Subjects who do not meet all inclusion criteria or meet any of the exclusion criteria will not be eligible for enrolment.

A subject will be assigned a subject number when the informed consent form (ICF) is signed. Any subject assigned a subject number but not enrolled in the study will be considered a screen failure.

In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required and will be reported in the electronic case report form (eCRF) including: Demography, Screen Failure details, Protocol Deviations, Eligibility Criteria, and any SAEs as defined in Section 6.4.1.

5.4. Withdrawal Criteria

A subject may withdraw from the study at any time at his/her own request and for any reason, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or administrative reasons. Reasons for premature discontinuation from the study will be recorded in the eCRF. Premature discontinuation from the study may result under the following circumstances:

- AE or SAE related to study procedures or the devices used in the study (AE/SAE section of eCRF must be completed)
- Protocol deviation
- Non-compliance with study procedures
- Subject lost to follow-up
- Subject withdraws consent
- Investigator discretion
- Sponsor terminates study

If a subject is prematurely discontinued from participation in the study for any reason, the investigator will make every attempt to perform an Early Withdrawal Visit (EWD). The EWD visit may be conducted as an in-clinic visit or by telephone. At a minimum if the EWD visit is conducted, AE/SAE data will be collected; other assessments may or may not be performed at the discretion of the investigator and consent of the subject. Upon discontinuation from the study, the subject will need to return the study devices.

If a subject's ALS progresses such that he/she is no longer able to attend the clinic for the scheduled visits, the subject may still continue in the study and continue with the home monitoring assessments. For subjects who miss a clinic visit or do not complete the home monitoring assessments, the following actions should be taken:

- The site must attempt to contact the subject and re-schedule as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned Time and Events schedule and ascertain whether the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

5.5. Subject and Study Completion

A completed subject is one who has completed the study through the Week 48 visit. The end of the study is defined as the last subject's last visit.

5.6. Treatment after the End of the Study

As this study does not involve treatment, subjects will not receive any post-study treatment from GSK after completion of the study. The investigator is responsible for ensuring consideration has been given to the post-study care of the subject's medical condition.

5.7. Concomitant Medications and Non-Drug Therapies

5.7.1. Permitted Medications and Non-Drug Therapies

Medications and non-drug therapies that are prescribed as part of the subject's ALS standard of care or for a concomitant medical condition are permitted and should be documented in the source documents. Any medication and non-drug therapy taken by the subject during the study from time of enrolment until their last visit in the study which, in the opinion of the investigator, might positively or negatively impact the movement/physical activity, heart rate or quantitative speech measurements will be recorded in the eCRF. In addition, any medication or non-drug therapy taken by the subject to treat AEs and SAEs which, in the opinion of the investigator, are related to a protocol-mandated procedure or one of the devices used in the study will be recorded in the eCRF. Medication name, dose, unit, frequency, route, indication, and dates of administration will be recorded in the eCRF.

5.7.2. Prohibited Medications and Non-Drug Therapies

There are no prohibited medications or non-drug therapies in this study. Enrolment into an investigational drug trial may however be prohibited if, in the opinion of the investigator and GSK medical monitor, the investigational drug might impact the objectives of this study.

6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

The timing of each visit and assessment in the Pilot Phase is listed in the Time and Events Table, Section 6.5, Table 1. Any repeat visits in this phase will be scheduled as needed.

The timing of each visit and assessment in the Core Study Phase is listed in the Time and Events Table, Section 6.5, Table 2. In this phase, all subject visits are scheduled relative to Baseline/Study Day 1. Should a visit be missed, visit dates should not be re-calculated from the date of the previous visit but should remain relative to Baseline/Study Day 1.

Visit windows have been identified and are specified in the Time and Events Tables, Section 6.5.

Supplementary study conduct information is provided in the Study Reference Manual (SRM). The SRM will provide site personnel with administrative and detailed information to complete the assessments.

6.1. Screening and Critical Baseline Assessments

The following assessments/data capture will be performed and the results recorded in the eCRF.

- Medical history. These data will be assessed in relationship to the inclusion/exclusion criteria listed in Section 5 and will help document other concurrent conditions which might impact the exploratory measures conducted in this study.
- ALS history, including type of ALS, muscle weakness onset date, ALS diagnosis date and ALS phenotype at onset. These data are important to help characterize the population enrolled in the study.
- Smoking history and current smoking status. These data are important to help interpret the quantitative speech measurement data.
- Demographic parameters of: year of birth, sex, race, and ethnicity. These data help define the population enrolled as well as help interpret the quantitative speech measurement data.
- A neurological examination will be performed according to local site protocol by medically qualified personnel. Functional regions involved (bulbar, cervical, thoracic, lumbosacral) limb symptoms (weakness, muscle atrophy, spasticity, hyperreflexia, and fasciculations); and presence or absence of bulbar and pseudobulbar symptoms will be recorded. These data are important for understanding the neurological phenotype of the ALS subjects being enrolled into the study. A brief neurological examination (presence or absence of weakness, hyperreflexia**,** and spasticity in each arm and leg, and presence or absence of bulbar and pseudobulbar symptoms) will be performed at the Pilot Screening Visit.
- Gold standard measures of function, specifically ALSFRS-R and FVC.
- Exploratory measures of movement/physical activity, HRV and speech.

6.2. Exploratory Measures and Assessments

Any trained staff at the study site can perform the exploratory measures and assessments. Appropriate training will be provided by GSK and MAT before the start of the study.

6.2.1. Reference Tasks

At present, the algorithms which will be used to process the movement/physical activity data are exploratory and non-validated. To help understand how the algorithms are performing in the ALS population as well as over time as the disease progresses, a series of reference tasks will be performed at each clinic visit in both the Pilot and Core Study Phases (See the Time and Events Tables, Section 6.5). These reference tasks will serve as a 'blueprint' for specific movements which the Faros sensor will measure. The data generated from these tasks will help understand if the algorithms are correctly measuring the specific activities and enable refinement and adaptation of the algorithms as required.

It is possible that during the course of the trial some of the reference tasks may no longer be necessary and dropped from the list as they are no longer informing algorithm development and refinement; therefore, the list is not fixed. Additionally, during the course of a subject's participation in the study, if a subject is unable to perform one of the reference tasks due to disease progression it may be omitted. The reference tasks may include the following movements/activities:

- Sitting
- Standing
- Lying down
- Walking
- Climbing stairs
- Transitions, such as: sit to stand, stand to sit, stand to lying, lying to stand
- Nine-hole peg test as a measure of arm dexterity

A detailed protocol on how to perform each reference task and how to manage the order of the tasks should a subject not be able to complete all of them will be provided in the SRM.

The data generated from the reference tasks will be utilized by MAT to confirm the performance of the algorithm and will not be transmitted to GSK for analysis. The following supportive data (brief neurological exam) will be captured in the eCRF: presence or absence of weakness, hyperreflexia, and spasticity in each arm and leg, whether the reference task was attempted, whether the reference task was completed according to the prescribed protocol, and use of walking aids.

6.2.2. Movement/Physical Activity

Movement/physical activity data will be collected by the Faros sensor throughout the study as described in the Time and Events Tables, Section 6.5. At each clinic visit in the Pilot and Core Study Phases, the Faros sensor will be placed on the subject just prior to the reference tasks and will be worn during completion of the tasks. The sensor will then be removed and sent home with the subject. The morning after the clinic visit, the subject will re-attach the sensor and wear it for approximately 3 days (except for the last visit where the subject will wear the sensor for 3 days before the visit). Additionally, in

between visits during the Core Study Phase the subject will wear the Faros sensor every month for approximately 3 days to enable data collection on a monthly basis over the 48 week study period.

Each subject will be issued one Faros sensor and 'LifeInsight Hub' for use during the study. The Faros sensor will be worn on the subject's chest on the sternum. Once attached, the Faros sensor should be worn continuously; however, it will need to be removed daily for charging. In the event of any skin discomfort or irritation the subject should remove the Faros sensor and contact the investigator for further instructions. Subjects will be provided instructions on how to operate and wear the Faros sensor and use the hub.

The raw movement and physical activity data will be processed by MAT. At present, the algorithms are exploratory. The processed data will be sent to GSK for final statistical analysis. The following supportive data will be captured in the eCRF: serial number of the Faros sensor and LifeInsight hub, date/time of sensor placement and removal, number of times the sensor fell off, subject activity level while wearing the sensor, subject's determination on ease of sensor set up and use, and subject feedback on whether the sensor impacted their activities of daily living or sleep habits. A diary will be provided to subjects as a tool to record details about their experience with attaching the sensor, how many times it fell off and their activity level while wearing the sensor.

6.2.3. Heart Rate Variability (HRV)

HRV data will be measured by the Fast Fix electrode patch throughout the study as described in the Time and Events Tables, Section 6.5. The Fast Fix electrode patch is worn with the Faros sensor on the subject's sternum according to the same schedule as the Faros sensor (see Section 6.2.2). The Fast Fix electrode patch will be replaced by the subject on a daily basis during the 3 day monitoring period. Subjects will be provided with a sufficient number of Fast Fix patches to cover each 3 day monitoring period. In the event of any skin discomfort or irritation the subject should remove the Fast Fix electrode patch and contact the investigator for further instructions. Subjects will be provided instructions on how to operate and wear the Fast Fix electrode patch.

HRV measures will be generated by MAT. The HRV measures will be sent to GSK for final statistical analysis. There are no additional supportive data specifically for the electrode patch other than what is already captured in the eCRF for the Faros sensor.

6.2.4. Quantitative Measure of Speech

Quantitative speech testing will be performed in the Core Study Phase as described in the Time and Events Table, Section 6.5, Table 2. Subjects will follow simple prompts on a computer screen instructing them to say a series of vowels, words, and paragraphs which will be recorded using a high definition digital microphone and stored securely on a laptop. The speech waveform data will be sent via secure method to MAT for processing. At present, the algorithms are exploratory. The processed data will be sent to GSK for final statistical analysis. The following supportive data will be recorded in the eCRF: serial number of the microphone, converter, and converter case, presence or

absence of bulbar and pseudobulbar symptoms, smoking history and current smoking status, age, gender and ethnicity.

6.3. Gold Standard Measures of Function

No study specific training or certification will be required for the gold standard measures of function. Sites should select appropriate, experienced personnel to perform these measures. The selected personnel would be expected to have experience performing these measures in the ALS population. In addition, level of experience necessary and conduct of the measures will be described in the SRM.

6.3.1. ALS Functional Rating Scale-Revised (ALSFRS-R)

The ALSFRS-R [Appendix 3] is a 12 item, validated questionnaire-based rating scale that assesses the functioning of ALS subjects across 4 domains: gross motor activity, fine motor activity, bulbar, and respiratory function [Cedarbaum, 1999]. The ALSFRS-R is recommended as a primary outcome measure for ALS clinical trials [EMA, 2013; De Carvalho, 2005; Leigh, 2004] and has been used in a number of recently conducted or ongoing studies [Cudkowicz, 2011]. The total ALSFRS-R score ranges from 0-48, with a lower score indicative of more severe impairment. Telephone administration of the ALSFRS-R has been validated [Kaufmann, 2007].

The ALSFRS-R will be collected in the Core Study Phase as described in the Time and Events Table, Section 6.5, Table 2. Telephone administration of the ALSFRS-R is permissible to accommodate the planned home visits as well as the planned in-clinic visits should the subject not be well enough to attend. Any site staff experienced and competent with the ALSFRS-R may administer the scale. A standardized ALSFRS-R scoring sheet will be provided to sites. Individual ALSFRS-R item scores will be recorded in the eCRF.

6.3.2. Forced Vital Capacity (FVC)

FVC is a measure of respiratory function and is the volume of air that can forcibly be blown out after a single, full breath. FVC is a sensitive measure of ALS disease progression, is used as a standard test for ALS management, and is recommended as a secondary outcome measure in ALS clinical trials [Cudkowicz, 2004; Czaplinski, 2006; Clavelou, 2013].

FVC will be collected in the Core Study Phase as described in the Time and Events Table, Section 6.5, Table 2 and will be performed by experienced site personnel according to local protocol using a calibrated spirometer. Every effort should be made to have the same individual perform the FVC for a given subject throughout the study. For each time point, the best FVC result (in liters) will be recorded in the eCRF.

6.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Tables, Section 6.5.

6.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

Only those AEs and SAEs which, in the opinion of the investigator, are related to a protocol-mandated procedure or one of the devices used in the study will be reported. The definitions of an AE or SAE can be found in Section 11.2, Appendix 2. The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

6.4.1.1. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs as defined above in Section 6.4.1 will be collected from the time a subject consents to participate in the study until the subject's last visit in the study (see Section 6.4.1.3), at the time points specified in the Time and Events Tables (Section 6.5).
- Medical occurrences that begin after obtaining informed consent but prior to the first protocol-mandated procedure may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 2.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to one of the protocol-mandated procedures or devices used in the study, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 2.

6.4.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence.

6.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 2.

6.4.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to either the protocol-mandated procedures or the devices is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met. GSK will report all device related

AEs and SAEs to the manufacturer for subsequent reporting to Medicines and Healthcare Regulatory Agency as appropriate. GSK will comply with country specific regulatory requirements relating to safety reporting to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

6.4.2. Device Incidents/Complaints

Should any malfunction or deterioration in the characteristics and/or performance of the devices used in this study be reported, GSK will promptly report them to manufacturer.

6.5. Time and Events Tables

Table 1 Time and Events – Pilot Phase

Procedures	Clinic Visit Screening Day 0	Home Monitoring (~ 3 days)	Telephone Contact[a] (TC)	Repeat Clinic Visit[b]	Home Monitoring[b] (~ 3 days)	Telephone Contact[a,b]	EWD
Informed consent	X						
Eligibility criteria	X						
Demography	X						
Medical and ALS history	X						
Brief neurological exam	X			X			
AEs/SAEs	X		X	X		X	X
Sensor placement	X	X		X	X		
Reference tasks	X			X			
Subject completes diary		X			X		
Site obtains diary information			X			X	X
Device impact questionnaire			X			X	X

a. Telephone contact to follow the 3-day home monitoring period to ensure the subject has completed the home monitoring period, diary, and to assess AEs, as appropriate. The expectation is that this call would occur on the first weekday following the home monitoring period.

b. May be repeated as necessary

Table 2 Time and Events – Core Study Phase

Study Day/Week[a]	Screen/Baseline Day 1/Week 0	Weeks 0, 4, 8	Week 12	Weeks 12, 16, 20	Week 24	Weeks 24, 28, 32	Week 36	Weeks 36, 40, 44, 48[c]	Week 48 or EWD
	Clinic Visit 1[b]	Home Monitoring (~3 days)	Clinic Visit 2	Home Monitoring (~3 days)	Clinic Visit 3	Home Monitoring (~3 days)	Clinic Visit 4	Home Monitoring (~3 days)	Clinic Visit 5
Procedures									
Informed consent	X[b]								
Eligibility criteria	X[b]								
Demography	X[b]								
Medical and ALS history	X[b]								
Neurological exam	X								
Smoking details	X		X		X		X		X
Brief neurological exam			X		X		X		X
AEs/SAEs[d]	X	X	X	X	X	X	X	X	X
Concomitant medications[e]	X	X	X	X	X	X	X	X	X
ALSFRS-R[e]	X	X	X	X	X	X	X	X	X
FVC	X		X		X		X		X
Speech assessment	X		X		X		X		X
Sensor placement	X	X	X	X	X	X	X	X	X
Reference tasks	X		X		X		X		X
Device impact questionnaire			X		X		X		X
Subject completes diary		X		X		X		X	
Site obtains diary information[f]		X	X	X	X	X	X	X	X
Follow-up Telephone Contact[g]		X		X		X		X	

a. Clinic visits and home monitoring periods should be conducted within ± 7 days of the scheduled visit/home period and should be scheduled according to the Baseline Visit.
b. Subjects transitioning from the Pilot Phase do not need to perform these procedures.
c. The Week 48 home monitoring period will occur the three days prior to the Week 48 in-clinic visit (Visit 5).
d. Assessed in clinic at Weeks 0, 12, 24, 36, and 48 and by telephone at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44.
e. Assessed in clinic at Weeks 0, 12, 24, 36, and 48 and by telephone at Weeks 4, 8, 16, 20, 28, 32, 40, and 44.
f. Diary information should be obtained by telephone at Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, and 44.
g. Telephone contact to follow each 3-day home monitoring period. The expectation is that this call would occur on the first weekday following the home monitoring period.

7. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee, and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.
- No data from this study will be used to inform clinical decision making for a subject's treatment or management.

8. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

8.1. Hypotheses

The study is designed to explore if there is a relationship between change from baseline in the physical activity/movement, heart rate and speech endpoints and change from baseline in the gold standard measures of function (ALSFRS-R and FVC).

8.2. Sample Size Considerations

8.2.1. Sample Size Assumptions

The study is intended to explore a number of physical activity/movement, heart rate and speech endpoints, but for the purposes of the sample size justification we will explore the relationship between the ALSFRS-R and one of the physical activity/movement endpoints, the total activity score.

With 20 subjects, we have an 80% chance of detecting a within subject correlation of greater than or equal to 0.6 (considered a moderate to strong correlation), if the true correlation is 0.7. The sample size is estimated based on statistical simulations conducted taking into account a number of assumptions outlined below regarding the two endpoints. The within subject correlation is calculated using the method suggested by Bland, 1995

Assumptions about the rate of decline in ALSFRS-R over time are estimated from a meta-analysis, performed by GSK, of nine similar ALSFRS-R trials from the literature. The limited biotelemetry data from stroke patients in the MAG104615 study has been used for the assumptions for the biotelemetry data. As this data was limited and in a different patient population, sensitivity to these assumptions are explored in Section

8.2.2. Total activity score is used as an example of one of the movement endpoints captured by the device.

In detail, the assumptions used in these simulations include:

- Both the ALSFRS-R and total activity score have a linear decline over time.
- The ALSFRS-R declines at a rate of 0.943 points per month. The variance of the rate of decline is assumed to be 0.771, and the within subject variance is assumed to be 4.
- The total activity score declines at a rate of 10 points per month. The variance of the rate of decline is assumed to be 0.6, and the within subject variance is assumed to be 10.
- The correlation between the two endpoints is assumed to take an auto-regressive structure, where within a subject at the same time point the two endpoints have a correlation of ρ while when the visits are i time points apart the correlation is assumed to be decreased to ρ^{i+1}.
- The correlation is assumed to be ρ=0.7.

8.2.2. Sample Size Sensitivity

Sample size sensitivity in Table 3 shows the probability of detecting a moderate to strong within subject correlation between the two endpoints, defined as a correlation greater than or equal to 0.6, for various scenarios regarding the strength of the true correlation and the variance of the decline for the total activity score. All the other sample size assumptions listed in Section 8.2.1 remain unchanged. As the variance of the slope is the main component in the total variance, exploration into changing the within subject variance had little impact on the probability of detecting a strong correlation and so the results are not presented here.

The probabilities are based on a simulation study carried out in R 2.15.2 with 10,000 simulated datasets per scenario.

Table 3 Probability of detecting a moderate to strong within subject correlation between the change from baseline in total activity score and the change from baseline in ALSFRS-R (N=20 subjects)

Correlation	Variance of decline	Probability of strong correlation (%)
0.8	0.6	83
0.7	0.6	80
0.6	0.6	80
0.8	0.7	83
0.7	0.7	80
0.6	0.7	79
0.8	0.8	83
0.7	0.8	80
0.6	0.8	79

8.2.3. Sample Size Re-estimation or Adjustment

There is no sample size re-estimation planned for this study.

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

Two populations are defined for this study:

- Enrolled population: This will consist of all subjects who have signed consent and are not a screen failure.
- Full Analysis Set (FAS): This will consist of all subjects with at least one post baseline measure for the ALSFRS-R and at least one physical activity/movement measure.

8.3.2. Interim Analysis

No formal interim analyses will be performed. Review of in stream data will be carried out to understand the utility of the measures and algorithms, the functionality of the data transmission process, and the durability and ease of use/acceptance of the selected accelerometer and electrode. Generated data may result in modifications to the study, such as: changes to the devices/equipment; repositioning of the accelerometer/electrode; modification to the algorithms, the supportive data collection plan or the data transmission process; dropping measures/tests which are not achievable.

8.4. Key Elements of Analysis Plan

8.4.1. Exploratory Analyses

As the purpose of the study is to be hypothesis generating, all analyses are considered exploratory.

A hierarchical approach will be used to focus the analysis on the endpoints where a correlation with either the ALSFRS-R or FVC (as applicable) is present. To begin with, the within subject correlation between the following endpoints will be explored using the analysis method detailed below:

- The change from baseline in the movement/physical activity endpoints as measured by the accelerometer device and the change from baseline in the ALSFRS-R
- The change from baseline in the heart rate endpoints as measured by the electrode device and the change from baseline in the ALSFRS-R
- The change from baseline in the speech endpoints and the change from baseline in the ALSFRS-R
- The change from baseline in the speech endpoints and the change from baseline in the FVC

An estimate of the between-subject correlation and the within-subject correlation will be obtained using the method described in Roy, (2006). The between-subject correlation will characterize whether subjects with greater decrease in the endpoint also tend to have the greater change in ALSFRS-R (or FVC). The within-subject correlation will describe whether a decrease in one endpoint within an individual is associated with a decrease in the other endpoint.

A mixed effect model with the change from baseline in the movement/physical activity endpoints and the change from baseline in the ALSFRS-R score as dependent variables will be fitted. An indicator variable to distinguish the two endpoints will be fitted as a fixed effect and a random effect. Other explanatory covariates will be fitted as fixed effects, as appropriate.

The RANDOM and REPEATED statements will be used to specify the structure of the covariance matrix for the two responses. The RANDOM statement will be used to specify an unstructured variance-covariance structure for the two responses. The REPEATED statement will be used to specify the variance covariance matrix for the error terms in the model. The structure of the variance covariance matrix is constructed by taking the Kronecker product of an unstructured matrix, which models the covariance for the two endpoints, with an unstructured or autoregressive (AR(1)) covariance matrix which models the covariance for the 2 repeated measures across visits.

As part of a sensitivity analysis, if the data allows the model to be fitted, a random intercept and slope will be specified in the RANDOM statement with an unstructured covariance matrix. Comparison between the model without and with the random intercept and slope will be assessed using the Bayesian information criteria (BIC).

If the data is not sufficient to allow for convergence of the model, then alternative variance covariance matrices may be considered. If convergence of the model parameters still cannot be achieved, the approach by Bland, 1995 will be used to estimate the within subject correlation.

Based on a predetermined rule that will be detailed in the Reporting Analysis Plan (RAP) further investigation of the endpoints may be carried out. This could include, but is not limited to:

- Summary statistics of the endpoints over time
- Plots of the individual subject change from baseline in the movement/physical activity, HRV and speech measures and the change from baseline in ALSFRS-R or FVC (as appropriate)
- A mixed model repeated measures (MMRM) analysis to characterize the change from baseline in the endpoint over time using an unstructured covariance matrix. If due to the limited number of subjects, the parameters of the unstructured covariance matrix cannot be estimated then other covariance structures will be considered. Covariates for baseline movement/physical activity, visit and a baseline by visit interaction will be included in the model. Where appropriate the results of the MMRM will be presented graphically. No imputation will be carried out for missing data.

Further details of the analyses will be specified in the RAP.

8.4.2. Other Analyses

Feedback from the subjects regarding the use of the sensor and electrode will be collected and summary statistics presented as appropriate.

8.4.3. Safety Analyses

The proportion of subjects reporting AEs related to a protocol-mandated procedure or the devices will be tabulated. A similar table for SAEs related to a protocol-mandated procedure or the devices will also be produced.

9. STUDY GOVERNANCE CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy. The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Written informed consent must be obtained from each subject prior to participation in the study. Depending on the ability of the subject to provide written informed consent, it may be necessary for verbal consent or assent to be obtained from the subject and written informed consent will then be obtained from the subject's legally acceptable representative, or caregiver on behalf of the subject (as per local requirements).
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

9.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

9.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

9.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any

institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

9.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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11. APPENDICES

11.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale - Revised
AR	Autoregressive
BIC	Bayesian Information Criteria
CONSORT	Consolidated Standards of Reporting Trials
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EWD	Early Withdrawal Visit
FAS	Full Analysis Set
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HF	High Frequency
HRV	Heart Rate Variability
ICF	Informed Consent From
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LF	Low Frequency
MAT	McLaren Applied Technologies
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effects Model Repeated-Measure Analysis
PII	Personally Identifiable Information
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event
SRM	Study Reference Manual
USB	Universal Serial Bus
WCBP	Women of Childbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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None

11.2. Appendix 2: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

11.2.1. Definition of Adverse Events

Adverse Event Definition:
• For this non-drug study, an AE is any untoward medical occurrence in a clinical investigation subject which, in the opinion of the investigator, is related to a protocol-mandated procedure or one of the devices used by the subject during the study.

11.2.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:
a. Results in death
b. Is life-threatening NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires hospitalization or prolongation of existing hospitalization NOTE: • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in disability/incapacity NOTE: • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.2.3. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the eCRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

11.2.4. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

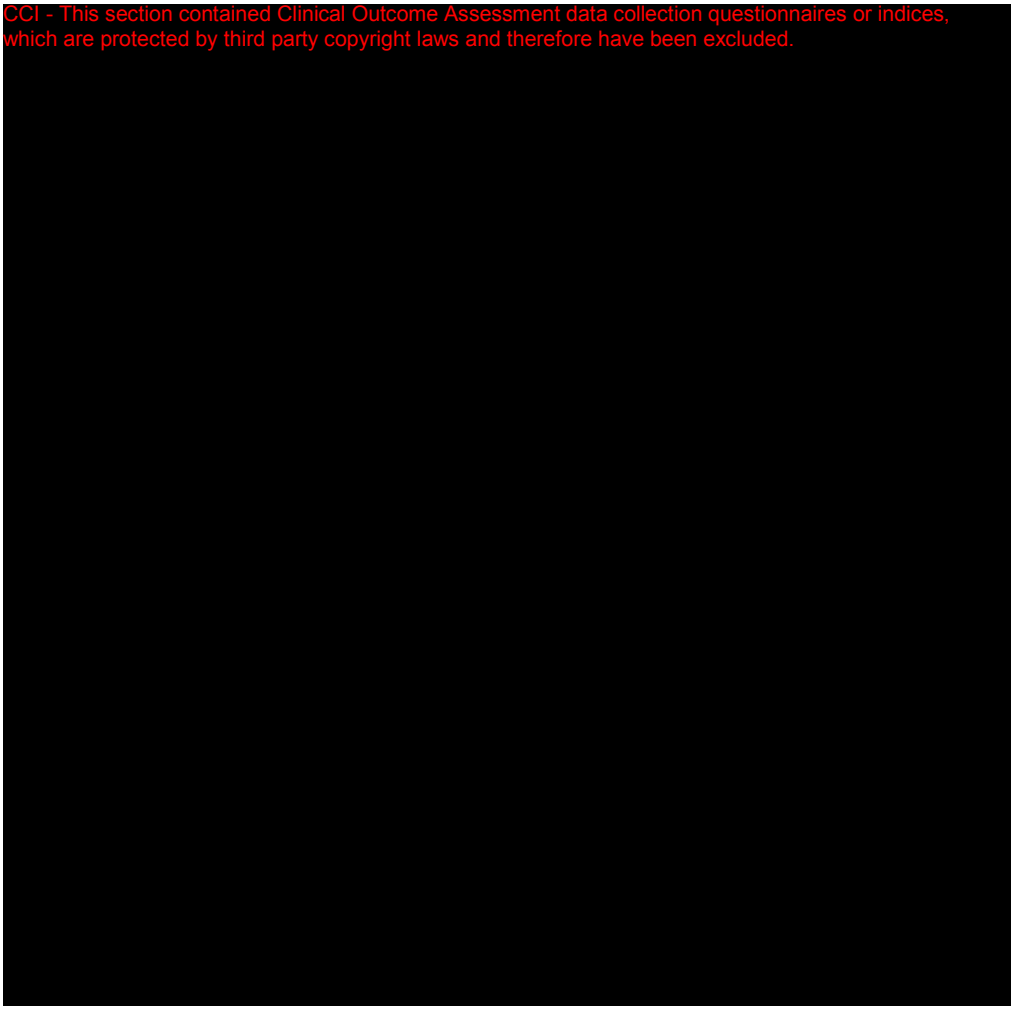
- The investigator is obligated to assess the relationship between the device or study-mandated procedure and the occurrence of each AE/SAE. Only those events which are considered to be attributable to either one of the devices or a study-mandated procedure will be reported in the eCRF.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes such as concomitant therapy, other risk factors, and the temporal relationship of the event to the procedure or device placement will be considered and investigated.
- The investigator will also consult the Participant Information Leaflet in the determination of his/her assessment.
- All AEs/SAEs considered attributable to one of the devices or a protocol-mandated procedure must be documented clearly in the medical notes by the investigator.
- If, based on follow up information, the investigator determines an AE/SAE is no longer attributable to either one of the devices or a protocol-mandated procedure, the event should be removed from the eCRF. The change in causality should be documented and retained in the medical notes.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. • The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period as a result of a device or study procedure related event, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

11.2.5. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool (eCRF). • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE coordinator. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72hrs of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the SAE coordinator by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

11.3. Appendix 3: ALS Functional Rating Scale - Revised (ALSFRS-R)



11.4. Appendix 4: Country Specific Requirements

No country-specific requirements exist.

11.5. Appendix 5: Protocol Changes

Amendment #1 09-APR-2015

This amendment applies to all sites in this study.

Summary and Rationale of Amendment Changes

This amendment is being made to: 1) clarify bullet #5 in Exclusion Criterion #3; 2) collect medications and non-drug therapies used to treat AEs\SAEs considered to be related to study procedures and/or devices in the eCRF; 3) include hyperreflexia on the full and brief neurological examinations; and to provide 4) further clarification or correction to other wording in the protocol.

List of Specific Changes

New text is identified by bolded wording and replaced/removed text is identified by strikethrough text.

Section 5.2, Exclusion Criterion #3

Exclusion criterion #3 was revised to remove an extraneous "or" in the fifth bullet:

Revised text:

3. Regionally restricted forms of ALS, or other atypical variants:

    - Isolated corticobulbar pattern of ALS with normal ambulation
    - Flail arm syndrome
    - Primary lateral sclerosis
    - Signs and chronic partial denervation restricted to a single limb
    - ALS ~~or~~ parkinsonism dementia complex

Section 5.7.1, Permitted Medications and Non-Drug Therapies

The wording has been revised to collect information on medications and non-drug therapies used to treat AEs and SAEs related to study procedures or devices in the eCRF. The wording has also been revised to reflect the medication data being collected in the eCRF (i.e., dose, unit, frequency, and route added).

Revised text:

Medications and non-drug therapies that are prescribed as part of the subject's ALS standard of care or for a concomitant medical condition are permitted and should be documented in the source documents. Any medication and non-drug therapy taken by the subject during the study from time of enrolment until their last visit in the study which, in the opinion of the investigator, might positively or negatively impact the movement/physical activity, heart rate or quantitative speech measurements, will be

recorded in the eCRF. **In addition, any medication or non-drug therapy taken by the subject to treat AEs and SAEs which, in the opinion of the investigator, are related to a protocol-mandated procedure or one of the devices used in the study will be recorded in the eCRF.** Medication name, **dose, unit, frequency, route,** indication, and dates of administration will be recorded in the eCRF.

Addition of hyperreflexia to the neurological and brief neurological examinations

The ALS symptom of hyperreflexia has been added to the neurological and brief neurological examinations, and wording has been added to differentiate between the neurological examination performed at the Core Screen/Baseline visit, and the brief neurological examination performed at the Pilot Screening visit and during the Core Phase of the study.

Section 6.1: Screening and Critical Baseline Assessments, fifth bullet, clarifications to the first and second sentences, and a fourth sentence added

Revised text:

- A ~~brief~~ neurological examination will be performed according to local site protocol by medically qualified personnel. Functional regions involved (bulbar, cervical, thoracic, lumbosacral) limb symptoms (weakness, atrophy, spasticity**, hyperreflexia,** and fasciculations); and presence or absence of bulbar and pseudobulbar symptoms will be recorded. These data are important for understanding the neurological phenotype of the ALS subjects being enrolled into the study. **A brief neurological examination (presence or absence of weakness, hyperreflexia, and spasticity in each arm and leg, and presence or absence of bulbar and pseudobulbar symptoms) will be performed at the Pilot Screening Visit.**

Section 6.2.1: Reference Tasks, fourth paragraph, second sentence

Revised text:

The data generated from the reference tasks will be utilized by MAT to confirm the performance of the algorithm and will not be transmitted to GSK for analysis. The following supportive data **(brief neurological exam)** will be captured in the eCRF: presence or absence of weakness**, hyperreflexia,** and spasticity in each arm and leg, whether the reference task was attempted, whether the reference task was completed according to the prescribed protocol, and use of walking aids.

Study Clarifications/Corrections

These changes are being made to clarify the intent of existing text and/or correct erroneous text.

Section 6.2.4 Quantitative Measure of Speech, sixth sentence

Revised wording to reflect the actual components more accurately, and to add the collection of the serial number for the converter case:

Revised text:

Quantitative speech testing will be performed in the Core Study Phase as described in the Time and Events Table, Section 6.5, Table 2. Subjects will follow simple prompts on a computer screen instructing them to say a series of vowels, words, and paragraphs which will be recorded using a high definition digital microphone and stored securely on a laptop. The speech waveform data will be sent via secure method to MAT for processing. At present, the algorithms are exploratory. The processed data will be sent to GSK for final statistical analysis. The following supportive data will be recorded in the eCRF: serial number of the microphone ~~and~~**,** converter, **and converter case**, presence or absence of bulbar and pseudobulbar symptoms, smoking history and current smoking status, age, gender and ethnicity.

Section 6.5, Time and Events, Table 1 and Table 2

Renamed "ALS symptom assessment" to "Brief neurological exam" in both Time and Event tables.

Original text:

ALS symptom assessment

New text:

Brief neurological exam

Section 7, Data management, third bullet

Removed the requirement to code the medical history data, as it was determined that an exemption to code the medical history information for this small, twenty-five subject study was not necessary, and that the listing of medical history terms would be sufficient for review and reporting.

Revised text:

Adverse events~~, medical history~~ and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug.

Protocol title

Remove the RAD prefix from the protocol title as the title should only include the numeric component.

Original text:

~~Study RAD201283:~~ An Exploratory Study to Investigate the Use of Biotelemetry to Identify Markers of Disease Progression in Subjects with Amyotrophic Lateral Sclerosis

Revised text:

An Exploratory Study to Investigate the Use of Biotelemetry to Identify Markers of Disease Progression in Subjects with Amyotrophic Lateral Sclerosis

Amendment #2 21-SEP-2015

This amendment applies to all sites in this study.

Summary and Rationale of Amendment Changes

This amendment is being made to: 1) modify the age requirement from 50 to 75 years to 18 to 80 years (Inclusion Criterion #1); 2) modify the time frame in Inclusion Criterion #3 from 12 months to 18 months between symptom onset and ALS diagnosis (and amend the description of the population accordingly); 3) clarify bullet 4 in Exclusion Criterion #3, 4) clarify that muscle atrophy is one of the limb symptoms to be included as part of the neurological examination, 5) to make other minor clarifications to the text.

List of Specific Changes

New text is identified by bolded wording and replaced/removed text is identified by strikethrough text.

Modification of the age requirement to 18 to 80 years (Inclusion Criterion #1)

The age range for entry into the study specified in Inclusion Criterion #1 was increased from 50 to 75 years to 18 to 80 years. This change, in conjunction with the other eligibility criteria of the protocol will ensure that the study population is representative of a broader ALS patient population without being restrictive, but at the same time is appropriate for the study objectives. .

Section 5.1, Inclusion Criterion #1

Revised text:

1. Between ~~50~~ **18** and ~~75~~ **80** years of age, inclusive, at the time of signing the informed consent.

Synopsis, Type and Number of Subjects

Revised text:

Male and female subjects ~~50~~ **18** to ~~75~~ **80** years of age with ALS will be enrolled into the study. Treatment of enrolled subjects will be consistent with local standard of clinical care for ALS patients. A maximum of 25 subjects will be enrolled such that approximately 20 subjects complete the study with 48 weeks of data.

Section 4.2, Type and Number of Subjects

Revised text:

Male and female subjects ~~50~~ **18** to ~~75~~ **80** years of age with ALS will be enrolled into the study. Treatment of enrolled subjects will be consistent with local standard of clinical care for ALS patients. A maximum of 25 subjects will be enrolled such that approximately 20 subjects complete the study with 48 weeks of data

Modification of the time frame in Inclusion Criterion #3 to 18 months between symptom onset and ALS diagnosis. The time frame between onset of symptoms and diagnosis of ALS was increased from 12 months to 18 months. The original timeframe was preventing subjects from entering the study who were part of the intended study population.

Section 5.1, Inclusion Criterion #3

Revised text:

3. Diagnosed with ALS within ~~12~~ **18** months of symptom onset.

Section 4.3.2, Population

Revised text:

The chosen population for study is a subset of the overall ALS population and consists of ALS subjects that have mild to moderate disease~~, are early in the disease,~~ and have a relatively high level of **clinical** function~~ing~~ at baseline. The selected population is expected to experience a functional decline during the 48 week study period of approximately 1 ALSFRS-R point /month (See Section 8.2.1). This level of decline **represents typical natural history of the disease and** is thought to be sufficient to start to understand the relationship between gold standard measures of clinical function and the novel measures of movement/physical activity, speech and HRV.

Section 5.2, Exclusion Criterion #3

Exclusion criterion #3 was revised to amend the word “and” to “of” in the fourth bullet to clarify the text.

Revised text:

3. Regionally restricted forms of ALS, or other atypical variants:

- Isolated corticobulbar pattern of ALS with normal ambulation
- Flail arm syndrome
- Primary lateral sclerosis
- Signs ~~and~~ **of** chronic partial denervation restricted to a single limb
- ALS parkinsonism dementia complex

Section 6.1, Screening and Critical Baseline Assessments, fifth bullet

This change is being made to clarify that muscle atrophy is one of the limb symptoms to be included as part of the neurological examination.

- A neurological examination will be performed according to local site protocol by medically qualified personnel. Functional regions involved (bulbar, cervical, thoracic, lumbosacral) limb symptoms (weakness, **muscle** atrophy, spasticity, hyperreflexia, and fasciculations); and presence or absence of bulbar and pseudobulbar symptoms will be recorded. These data are important for understanding the neurological phenotype of the ALS subjects being enrolled into the study. A brief neurological examination (presence or absence of weakness, hyperreflexia**,** and spasticity in each arm and leg, and presence or absence of bulbar and pseudobulbar symptoms) will be performed at the Pilot Screening Visit.

Study Clarifications

These changes are being made to clarify the existing text.

11.5.2.1 Heart Rate Variability (HRV)

Autonomic function is known to be impaired in ALS [Pavlovic, 2010; ~~Mega Electronics Ltd, 2014~~; Merico, 2011; Pinto, 2012].

Section 4.3.3.3, Speech

Revised text:

Speech is produced as a result of muscle and respiratory function [Green, 2013], **which are both affected in ALS**. ALS results in progressive bulbar motor deterioration leading to impaired speech and swallowing and complications from these bulbar symptoms can significantly impact survival [Green, 2013]. Pseudobulbar manifestations may also contribute to speech impairment. Speech measurement is part of the assessment of bulbar function in ALS; however, many of the available tests do not provide meaningful information on disease progression [Green, 2013]; therefore, an easy to use, quantitative measure of speech might be a meaningful endpoint for monitoring ASL disease progression.

Section 4.3.3.4, ALSFRS-R and FVC

Revised text:

ALSFRS-R is a gold standard measure of functional decline in ALS and is routinely used to monitor disease progression and evaluate treatment effects in clinical trials and in clinical practice [Brinkmann, 1997; Cudkowicz, 2004; **Cedarbaum, 1999**]. In order for any new outcome measure to be clinically meaningful and relevant to physicians and regulators, it will need to correlate to the ALSFRS-R.