Eye Muscle Needle Electromyogram (EMu) Pilot Study Protocol

A data collection and analysis pilot study to indicate preliminary characterisation of the electromyogram signal in relation to needle position with respect to the extraocular muscles, as observed during electromyogram needle guided treatment of strabismus in adults

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STUDY COORDINATION CENTRE: Royal Liverpool Hospital, RLBUHT

IRAS Project ID: 249119

Study Team

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Statistician:	Dr Antonio Eleuteri, Statistician, Royal Liverpool Hospital
Study Manager:	Dr Tristan Payne, Clinical Scientist, Royal Liverpool Hospital

Study Coordination Centre

For general queries, supply of Study documentation, and collection of data, please contact:

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Clinical Queries

Clinical queries should be directed to Dr Payne who will direct the query to the appropriate person.

Sponsor

The Royal Liverpool and Broadgreen University Hospitals NHS Trust is the research Sponsor for this Study. For further information regarding the sponsorship conditions, please contact:

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Funder

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STUDY SUMMARY

This protocol describes the **EMu Pilot Study** and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the Study. Problems relating to this Study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition) and Good Scientific Practice (Version 1). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

GLOSSARY OF ABBREVIATIONS

HRA	Health Research Authority
REC	Research Ethics Committee
EMG	Electromyogram
EOM	Extraocular muscle
BTX	Botulinum toxin

KEYWORDS

Extraocular muscle, electromyogram, monopolar, needle guidance, Botulinum toxin, strabismus

TITLE

A data collection and analysis pilot study to indicate preliminary characterisation of the electromyogram signal in relation to needle position with respect to the extraocular muscles, as observed during electromyogram needle guided treatment of strabismus in adults

DESIGN

A cross-sectional observational pilot study

AIMS

Gain more knowledge of the electromyogram acquired during electromyogram (EMG) needle guided treatment of strabismus, indicate the feasibility of improving the technology and inform a larger study to provide evidence to underpin the development of such new technology.

OUTCOME MEASURES

Primary

- The change in the EMG signal as the needle approaches, and enters, the target extraocular muscle.

Secondary

- Clinician's score of the step change from baseline EMG to 'active' EMG level heard immediately prior to delivery of Botulinum toxin (BTX);
- Clinician's score of their confidence in accurate needle placement;
- Clinician's score of overall quality of the EMG signal heard during the procedure;
- Change in patient's angle of deviation following treatment.

POPULATION ELIGIBILITY

Adults undergoing planned, routine EMG needle guided BTX injection into either lateral or medial rectus muscle for the treatment of strabismus.

DURATION

Up to 20 weeks.

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1 INTRODUCTION

1.1 BACKGROUND

1.1.1 Strabismus, Botulinum toxin and EMG

Strabismus is an ocular condition caused by unbalanced contraction of EOMs, specifically the medial or lateral rectus muscle. There are several functional consequences of the condition, and significant negative psychosocial effects that reduce quality of life (Durnian et al., 2011). In some cases, strabismus is treated with injections of BTX to temporarily inhibit the medial or lateral rectus muscle responsible for the excessive deviation of the globe, thus straightening the gaze.

The EOMs are histologically unique, being the only muscles in humans containing both slow fibres *and* fast-twitch fibres. Consequently, the motor unit potentials generated by EOMs are also unique, being of much lower amplitude and duration, and with a higher firing rate when compared to peripheral skeletal muscles (Björk, 1952).

Due to the deep location of the rectus muscles, the needle used to deliver BTX cannot be easily guided without assistance. The unique electrical activity of the EOMs described above is harnessed in combination with EMG needle guidance to help ensure the toxin is delivered correctly.

1.1.2 Current practice

An early publication described the application of EMG needle guidance in treating strabismus with BTX, whereby a needle electrode was used to pick up the EMG activity at the injection site, and by amplifying and playing the EMG signal through a loudspeaker, the clinician could learn to identify the correct location from the sounds. In this paper, Scott (1981) states “one learns to differentiate the low amplitude distant signal from the high amplitude and crackling sound when the centre of the muscle is reached”. The sound is also described as “rain on a tin roof” (Childers, 2003), and the increase in EMG volume together with the change in sound are discerned by the clinician as the patient gazes in the direction of the dystonic muscle into which the BTX is injected, thus activating the muscle.

Practice commonly observed today has not changed in the intervening 37 years. Today, as then, the sound is provided by a simple device that amplifies the EMG signal at the tip of the needle through with the BTX will pass when it is injected, and plays it through a loudspeaker. Devices today may also provide an indication of the signal level and/or the waveform morphology.

1.1.3 Existing research

There is very little research exploring the technology described above, and how it may be improved in the context of strabismus. Techniques with potential for improving EMG guidance include:

- *Visualisation of the waveform*. Kim et al. (2011) published a method of displaying the EMG

waveform to the clinician during delivery of BTX to treat strabismus. Kim et al. suggest displaying the waveform delivers an increase in accuracy and decrease in procedure time, although do not detail how this was achieved or measured.

- *Motor unit potential rise time*. Ajax et al. (1998) used a threshold applied to the motor unit potential rise time to determine correct positioning within limb muscles. They showed an improvement in localisation of the needle under EMG guidance compared to anatomic localisation.

- *High-pass filtering to remove noise*. Brown et al. (2010) performed experiments with rotator cuff muscles, and related signals from needle electrodes to signals from surface electrodes. They found that there was still good correlation between the two signals even when low frequency components of the surface signal below 240 Hz were removed. If, by extension, this applies to EOMs that contain even higher frequency components, then high-pass filtering may reduce interference without degrading the information from the target muscle.

- *Measuring parameters of the EMG spectrum*. Early research by Trimble et al. (1973) characterised the spectrum of an averaged extraocular motor unit potential, and found a peak around 900 Hz, in contrast to a high prevalence of much lower frequencies in skeletal muscles. Despite this evidence, Hunter et al. (1996), in a study of only 23 patients, did not find correlation between effectiveness of strabismus treatment and three basic parameters of the spectrum: tallest peak, peak frequency and total power. This may be due to the different electrode types used – Trimble et al. used coaxial electrodes capable of detecting more localised EMG than the monopolar electrode used by Hunter et al. However, recent unpublished evidence gathered at Medical Physics and Clinical Engineering, Royal Liverpool Hospital, using thread electrodes does suggest high frequency components of the EMG signal relate to EOM activity.

- *Interference analysis*. Werdelin et al. (2011) used bipolar electrodes with previously reported turn amplitude analysis (TAA) to guide BTX injections for the treatment of torticollis. The injection was performed subsequently to the analysis, suggesting TAA may not be achievable in the case of monopolar needle EMG.

- *Signal decomposition*. Decomposition of the EMG signal may allow single motor unit activity to be detected and characterised. Although reported using concentric (bipolar) needle electrodes (Pham et al., 2014), this technique may be useful in the analysis of monopolar EMG signals.

The publications above indicate possible improvements to the technology; however, the evidence is sparse and inconclusive in the context of EMG needle guided treatment of strabismus.

Specifically, while the EMG of individual motor units is well characterised, when monopolar needles of the type used in EMG guided BTX injections are used, the EMG signal represents the contribution of many motor units, and is not so readily interpreted.

1.2 RATIONALE FOR CURRENT STUDY

The rather imprecise "rain on a tin roof" identification of the EMG signal described above for what is a precise procedure – the medial and lateral rectus muscles are around 2.5 mm to 4.7 mm in diameter – will arguably negatively impact on treatment efficacy and repeatability. There may also be an increase in the likelihood of side effects such as ptosis and vertical deviation when the toxin spreads beyond the target muscle. When the needle is guided with direct observation into the muscle belly, the number of cases of ptosis is as low as 1 in 32 cases (Wan et al., 2011), suggesting the higher rates generally observed with EMG guidance are due to suboptimal positioning of the needle. Furthermore, if more toxin is used where injection takes place distal to the optimum location, the result may be an increase in antibody formation and reduced response to the toxin. It is also difficult to teach the effective use of EMG needle guidance where such descriptive interpretation is involved.

The need for improvement was confirmed during recent research of consensus needs of a group of clinicians (Payne, 2016), which distilled specific needs relating to EMG needle guidance in this context. Four of these are particularly challenging and of interest for this study:

1) Isolating the EOM EMG signal by reducing contamination from other muscles;
2) Displaying the confidence that the needle is within the EOM;
3) Indicating the proximity of the needle to the EOM;
4) Providing a signal quality score.

Clinicians ranked the first two as higher priority than the third and fourth. Note that all are dependent upon learning more about the EMG signal characteristics that are affected by distance of the needle to the target muscle.

Despite the need, commercially available handheld EMG monitors of the type typically used to guide injections in this context do not appear to assist the clinician by isolating the extraocular EMG signal from interfering EMG signals, nor do they process the EMG signal to provide additional information such as confidence of location or proximity to the EOM. This presents a potential opportunity to develop the technology and deliver benefits to patients with improved treatment efficacy.

Considering this clear need for improvement, there is currently little evidence to support development of the EMG guidance technology used to treat strabismus with BTX. Detailed analysis of extraocular muscle EMG obtained using a monopolar needle electrode is needed to identify feasible approaches in improving EMG needle guidance.

This pilot study is an exciting opportunity to gain more knowledge and explore the hypothesis that there is a relationship between characteristics of the EOM EMG signal and the proximity of the needle to the rectus muscle belly. This knowledge may then be used to develop a new needle guidance technology, potentially paving the way for far less subjective evaluation of the "rain on a tin roof" sound.

2 STUDY OBJECTIVES

The principal objective is to identify any signal characteristics that could potentially be indicative of the location of the EMG needle with respect to the target muscle.

A secondary objective is to indicate the value of developing the technology of EMG needle guidance in this application, and inform the design of any future research.

3 STUDY DESIGN

This is a cross-sectional observational study.

3.1 MATERIALS

The key equipment and software required are:

- EMG Signal Capture System, comprising:
  - A USB powered bio-signal acquisition device to capture the EMG signal;
  - A buffer device to allow the EMG signal to be detected;
  - A USB camera (webcam) to record audio and video of the procedure;
  - An office laptop to drive the signal acquisition device and camera;
  - Acquisition software to capture the EMG signal and event markers;
- R software environment for statistical computing and graphics.
- MATLAB software environment for data analysis and software development.

Further details of the EMG signal capture system, including specification analysis, are in APPENDIX 1: EMG SIGNAL CAPTURE SYSTEM.

3.2 METHOD

The study involves recording data during routine treatment of strabismus using EMG guided needle injection of BTX. The current procedure involves amplifying the EMG signal detected at the needle, which is used by the clinician to guide the needle. The pilot study will record this EMG signal onto computer, in addition to some other data available during or after the procedure. The data to be captured is:

Data	Detail	Justification
EMG signal	EMG signal throughout procedure, from just prior to initial contact of needle with conjunctiva through to final withdrawal of needle from conjunctiva following delivery of BTX	To facilitate processing and analysis of EMG waveform
Needle event markers	The points in the recording when: the needle contacted the conjunctiva; where the needle is considered by the clinician to be 'on target'; when BTX was delivered; and when the needle	To help distinguish 'on target' and 'off target' regions of the EMG waveform

	was withdrawn	
Audio / video recording	An audio and video recording of the procedure showing needle position and patient's eye position	To help distinguish 'on target' and 'off target' regions of the EMG waveform
Clinical scores	Post-procedure, the clinician's score of: • The step change from baseline EMG to 'active' EMG level heard immediately prior to delivery of BTX, from 1 to 5: 1 – No significant step change heard; 2 – Possible step change heard, not at all clear; 3 – Unambiguous step change but not clear; 4 – Somewhat clear step change heard; 5 – Very clear step change heard. • Confidence in accurate needle placement, as a percentage; • Overall quality of the EMG signal heard during the procedure, from 1 to 5: 1 – Signal not present 2 – Poor quality 3 – Adequate quality 4 – Good quality 5 – Excellent quality	To help evaluate signal processing and statistical analysis outcomes
Patient / procedure meta-data	• Patient age • Units of BTX injected • The target muscle (lateral or medial, left of right) • Any known contraindications to optimal EMG needle guidance, e.g. scar tissue around the target muscle • Whether: ○ The patient is repeat or 'routine', where no follow-up is planned and the patient has been seen at least once before for the same treatment; or ○ The patient is 'new', and has not previously received BTX for the treatment of strabismus by Mr Yagan. • Approximate distance between the centre of the reference skin electrode and the needle insertion point • The outcome of the routine skin electrode impedance check	To include potential characteristics for statistical analysis and help identify potential causes of outliers
Patient pre-	Typically measured in units of prism dioptres	To allow comparison of signal

treatment angle of deviation		characteristics with the amount of improvement in deviation, and help evaluate signal processing and statistical analysis outcomes

There will also be follow-up for each patient, within four weeks, but typically around two to three weeks following treatment. This is current practice for new patients and is an additional requirement for repeat patients. The data recorded during the follow-up is:

Data	Detail	Justification
Patient post-treatment angle of deviation	Typically measured in units of prism dioptres	To allow comparison of signal characteristics with the amount of improvement in deviation, and help evaluate signal processing and statistical analysis outcomes

Once the data has been captured, processing and statistical pattern recognition of the recorded data will address the study objectives.

Duration: up to 20 weeks. Mr Yagan's clinic takes place every two weeks and each list includes approximately seven patients. If five successful recordings are made per clinic, 25 recordings will be made over a period of 10 weeks; allowing an additional four weeks for follow-up and four weeks contingency equates to 20 weeks. Data processing and analysis will take place once the study has ended. See Section 9.2 for a Gantt chart.

Subjects: Signals will be recorded from 25 adult patients receiving treatment for strabismus with EMG guided injection of BTX.

3.3 LOCATION

All recording will take place at:

Manchester Royal Eye Hospital
Oxford Road
Manchester M13 9WL.

Data processing and analysis will take place at:

Medical Physics & Clinical Engineering
Royal Liverpool Hospital
Royal Liverpool & Broadgreen University Hospitals NHS Trust
Duncan Building, 1st Floor
Prescot Street

Liverpool L7 8XP.

3.4 PERSONNEL

The procedure being observed will be carried out by Mr Yagan. There are no training needs identified for this protocol.

Pre-treatment and post-treatment angle of deviation measurements and other patient data as required by the Method will be provided by an orthoptist. There are no training needs identified for this protocol.

The data recording will be carried out by Dr Payne. There are no training needs identified for this protocol.

Data analysis will be carried out by Dr Antonio Eleuteri. There are no training needs identified for this protocol.

3.5 STUDY OUTCOME MEASURES

3.5.1 Primary

- The change in the EMG signal as the needle approaches, and enters, the target extraocular muscle.

3.5.2 Secondary

- Clinician's score of the step change from baseline EMG to 'active' EMG level heard immediately prior to delivery of BTX;
- Clinician's score of their confidence in accurate needle placement;
- Clinician's score of overall quality of the EMG signal heard during the procedure;
- Change in patient's angle of deviation following treatment.

4 PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

None, since this is an observational study.

4.2 INCLUSION CRITERIA

i. Adults undergoing planned, routine EMG needle guided BTX injection into either lateral or medial rectus muscle for the treatment of strabismus.
ii. Patients being treated by Mr Yagan. This criterion will optimise consistency of recorded data, especially clinician's opinion of needle placement and EMG signal quality.

4.3 EXCLUSION CRITERIA

Patients with Chronic progressive external ophthalmoplegia (CPEO) are excluded; a highly attenuated EMG signal is expected.

4.4 WITHDRAWAL CRITERIA

Should the injection not be delivered for any reason, the participant will be withdrawn from the study.

5 ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – 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
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Potential **Adverse Events**:

i. EMG recording system interferes with existing EMG monitor used to guide the needle, preventing delivery of treatment. In this case, the EMG recording system will be immediately disconnected from the EMG monitor and the procedure resumed.

Potential **Serious Adverse Events**: none identified.

5.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.2.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.2.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the North West – GM South REC where in the opinion of the Chief Investigator, the event was:

- 'related', i.e. resulted from the administration of any of the research procedures; and
- 'unexpected', i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs

Fax: 0151 706 5803, attention Tristan Payne

Please send SAE forms to:

Medical Physics & Clinical Engineering
Royal Liverpool Hospital
Royal Liverpool & Broadgreen University Hospitals NHS Trust
Duncan Building, 1st Floor
Prescot Street
Liverpool L7 8XP
Tel: 0151 706 4223 (Mon to Fri 09.00 – 17.00)

6 ASSESSMENT AND FOLLOW-UP

Follow-up for each patient is as set out in the Method (Section 3.2).

7 STATISTICS AND DATA ANALYSIS

EOM EMG signals will be characterised by time series analysis methods [14]:

- Plotting
- Estimation of autocorrelation function
- Estimation of spectral density (to separate short-term and seasonal effects)
- Model identification (information criteria)
- Model fit (ARMA processes)

Regression analysis techniques [15] will be employed to assess the relationships between EMG signal

characteristics (to be defined) and position of needle with respect to target location in EOM.

An ordinal logistic regression model will be designed to estimate the expected value of the scores conditional on signal characteristics.

Given the expected sample size of 25 subjects, it's possible to empirically assess the maximum number of signal characteristics that can be used in the model formulation as $1/10^{th}$ of the sample size [15], i.e. 2 parameters (assuming an even spread of the scores across the subjects).

Wald statistics and the Akaike Information Criterion will be used to assess the goodness of the fit, and discrimination and calibration measures of accuracy of the model will be estimated by bootstrap resampling.

8 REGULATORY AND QUALITY ISSUES

8.1 SAFETY

Risks to the patient and users of the EMG Capture System have been controlled through application of Medical Physics and Clinical Engineering's Risk Management Procedure CD1451, which complies with BS EN ISO 14971:2012 – Risk Management for Medical Devices.

8.2 ETHICS APPROVAL

The Chief Investigator has obtained approval from the North West – Liverpool East Research Ethics Committee and Health Research Authority (HRA) approval. The study will be submitted to each proposed research site for Confirmation of Capacity and Capability. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

The approving body will be kept informed as in Section 8.11.

The ethical considerations of the project are viewed as minimal for the following reasons:

- The study is non-interventional;
- There is low impact on study participants, including a small change to procedure, an additional person present during the procedure and in some cases an additional follow-up visit;
- There are no after-effects of participation;
- The participant is not required to interact for the purposes of the study.

8.3 CONSENT

Before the clinic session, an orthoptist will review the patient records for eligibility to enter the study. Patients are seen by the orthoptist prior to the procedure as part of standard care. During this pre-procedure appointment, if the patient is eligible to participate in the study, the study will be explained to them and

they will be invited to take part. They will be offered the Participant Information Sheet to read while they wait for the procedure, and will have at least 15 minutes to decide if they wish to take part. Before the clinical procedure, the ophthalmologist Principal Investigator will address any questions or concerns, and if they wish to take part, obtain signed consent from the participant. The Chief Investigator will securely hold a copy of the consent forms. The right of the participant to refuse to participate without giving reasons shall be respected.

After the participant has entered the study, the ophthalmologist remains free to deviate from the protocol at any stage if he feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases, the participants remain within the study for the purposes of follow-up and data analysis.

All participants are free to withdraw at any time from the study without giving reasons and without prejudicing further treatment. If a participant withdraws their consent to take part in the study, their personally-identifiable data will be securely deleted; any anonymous data already collected will be retained.

8.4 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and will abide by the General Data Protection Regulation.

All patient data including identifiable audio / video recordings will be recorded directly onto an encrypted laptop drive during the clinic. After each clinic, the laptop and encrypted data stored on it will be physically transported by the Chief Investigator from Manchester Royal Eye Hospital to Royal Liverpool Hospital for processing and statistical analysis. The data will be transferred from the laptop to the local NHS computer network as soon as practicable after the clinic, and the data immediately removed from the laptop encrypted drive.

All data will be held by Medical Physics and Clinical Engineering, Royal Liverpool Hospital on secure, password protected and firewalled network facilities provided by the department. Security arrangements include nightly backups and access controls to restrict access to those who need it. Analysis will be carried out within Medical Physics and Clinical Engineering, Royal Liverpool Hospital, by the Chief Investigator (Dr Payne) and the Statistician (Dr Eleuteri). Personal, identifiable data will only be used for this study, and all steps reasonably necessary will be taken to ensure such data will only be disclosed to those involved in the study that have a need in relation to this study.

Within three months of the end of the study, following analysis of the data, all personal identifiable data will be destroyed. Video recordings will be deleted, and any identifiable or pseudonymous participant identifiers will be removed. All deleted data will also be removed from any backups. The remaining anonymous data will be stored securely for three years, after which it will be destroyed; similarly, it will be removed from any backups. The anonymous data will be held for this period as it may contribute to a further, larger study if this pilot study indicates that additional research is required. This may reduce the

number of participants required in subsequent research.

The data custodian will be Dr Tristan Payne, Royal Liverpool Hospital.

8.5 INDEMNITY

This study is covered by NHS indemnity.

8.6 SPONSOR

The Royal Liverpool and Broadgreen University Hospitals NHS Trust will act as Sponsor for this study. It is recognised that as an employee of the Trust, the Chief Investigator has been delegated specific duties, as detailed in the Sponsorship Approval letter.

8.7 FUNDING

Medical Physics and Clinical Engineering, Royal Liverpool Hospital are funding direct costs and Royal Liverpool staff opportunity costs.

8.8 AUDITS

The study may be subject to inspection and audit by Royal Liverpool and Broadgreen University Hospitals NHS Trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

8.9 REGULATORY APPROVAL

The study is not required to be registered with the MHRA as it is not a clinical investigation of a new medical device.

8.10 LOCAL APPROVAL

Local approval will be sought from Royal Liverpool Hospital and Manchester Royal Eye Hospital Research & Development departments following local procedures.

8.11 COMMUNICATION PLAN

Stakeholders will be kept informed by the Chief Investigator as follows:

Activity	Principal Investigator at Manchester Royal Eye Hospital	Royal Liverpool R&D (Sponsor)	Manchester Royal Eye Hospital R&D	Health Research Authority
Study protocol	Consult	Seek approval	Seek approval	Seek approval

Non-substantial deviations[1] from protocol	Consult	Inform	Inform	Inform at end of study
Substantial deviations from protocol	There will be no intentional substantial deviations from the protocol. Substantial changes must be made by approved amendment to the protocol. Any unintentional substantial deviations will result in the study being suspended while the Ethics Committee is informed and a protocol amendment made if appropriate.			
Non-substantial changes[2] of any documentation already approved by the Ethics Committee	Inform	Inform	Inform	Inform
Substantial changes[3] (amendments) of any documentation already approved by the Ethics Committee	Consult	Seek approval	Seek approval	Seek approval
Premature ending of the study	Consult	Inform	Inform	Inform
Planned end of study	Inform	Inform	Inform	Inform
Outcome of study	Inform	Inform	Inform	Inform

8.12 PROTOCOL AMENDMENTS

Amendments to this protocol will be subject to approval as set out in the Communication Plan (Section 8.11).

The protocol version (m.n) will be updated in the event of any change after version 1.0, the first externally communicated. Minor changes will be identified by increase to *n*, while major version updates will be identified by an increase to *m*.

8.13 STUDY EVALUATION

Following completion of the study, the study will be evaluated by reflecting on the process and outputs as an opportunity for learning and future improvement. The Chief Investigator is responsible for carrying out

[1] Not affecting the rights, safety and well-being of human subjects and not related to the study objectives or endpoints

[2] e.g. minor logistical or administrative changes, telephone numbers, renewal of insurance

[3] Affecting patient's rights, safety and well-being, or the scientific integrity of the study

the evaluation, which will ideally take the form of a reflective meeting with those involved.

8.14 RISKS TO COMPLETION OF STUDY

Impact	Low	Medium	High
High	Sponsorship cannot be agreed		
Medium	EMG Capture System is not suitable for the intended environment	Patients are not recruited at anticipated rate due to lower than expected throughput of clinic, or fewer patients consent to recording of data	
Low			

Probability

Mitigating actions are:

- Sponsorship cannot be agreed: sponsorship to be sought at earliest opportunity from Royal Liverpool Hospital.
- Patients are not recruited at anticipated rate: three week contingency included in time scales.
- EMG Capture System is not suitable for the intended environment: the system will be tested in the intended environment before the first patient is recruited to identify any use or environmental issues.

8.15 QUALITY PLAN

In developing the EMG Capture System, a design lifecycle process will be followed using Medical Physics & Clinical Engineering Quality Management System procedures and templates where available, including:

i. Requirements Analysis, capturing the needs of this study on the EMG Capture System.
ii. Requirements Specification, capturing the technical and quality requirements of the EMG Capture System.
iii. Design, capturing the choice of components to the EMG Capture System.
iv. Build.

v. Design Verification, testing the technical performance of the solution.
vi. Design Validation

Risks will be managed by following the Department's Risk Management Procedure, as discussed in Section 8.1.

The project will be managed as described in this protocol.

9 STUDY MANAGEMENT

9.1 RESOURCES

At Manchester Royal Eye Hospital, required practical provisions are:

- Access to the clinical procedure room for the duration of the clinic;
- Space to accommodate the EMG Signal Capture System, camera and researcher operating the system;
- Provision for follow-up assessment of patients.

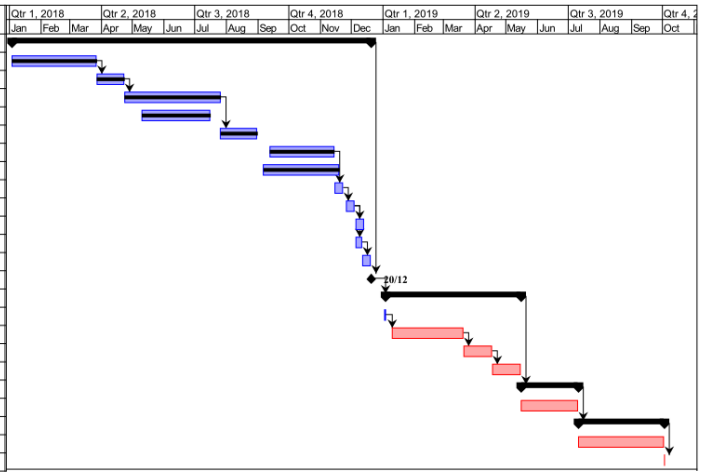
At Liverpool Royal Hospital, provisions are made for:

- Data processing and pattern recognition software, as required;
- Secure storage of data.

The day-to-day management of the study will be coordinated by the Chief Investigator at the Royal Liverpool Hospital.

9.2 TIMESCALES

Name	Duration	Start	Finish
Planning and Approvals	**252 days**	**03/01/18 08:00**	**20/12/18 17:00**
Protocol Preparation	60 days	03/01/18 08:00	27/03/18 17:00
Intention to Sponsor Agreement	20 days	27/03/18 08:00	23/04/18 17:00
HRA Approval Application (IRAS)	69 days	23/04/18 08:00	26/07/18 17:00
Peer Review	48 days	10/05/18 08:00	16/07/18 17:00
Provisional REC Approval (PR)	27 days	26/07/18 08:00	31/08/18 17:00
MHRA Query - Device Study	46 days	12/09/18 08:00	14/11/18 17:00
Manchester Medical Engineering Approval	53 days	06/09/18 08:00	19/11/18 17:00
Local approval IRAS Form with REC changes	7 days	15/11/18 08:00	23/11/18 17:00
HRA Approval	7 days	26/11/18 08:00	04/12/18 17:00
Manchester Trust RD&I Approval, Letter of Access	7 days	05/12/18 08:00	13/12/18 17:00
Sponsor approval to proceed	5 days	05/12/18 08:00	11/12/18 17:00
Contingency	7 days	12/12/18 08:00	20/12/18 17:00
All approvals in place - study ready to start	0 days	20/12/18 17:00	20/12/18 17:00
Study Stage 1: Data Capture	**95 days**	**03/01/19 08:00**	**15/05/19 17:00**
Medical Engineering Electrical Safety Tests	1 day	03/01/19 08:00	03/01/19 17:00
Patient Recruitment and Data Recording	50 days	10/01/19 08:00	20/03/19 17:00
Patient follow-up buffer	20 days	21/03/19 08:00	17/04/19 17:00
Contingency	20 days	18/04/19 08:00	15/05/19 17:00
Study Stage 2: Data Analysis	**40 days**	**16/05/19 08:00**	**10/07/19 17:00**
Signal processing and statistical analysis	40 days	16/05/19 08:00	10/07/19 17:00
Dissemination	**60 days**	**11/07/19 08:00**	**02/10/19 17:00**
Paper preparation and submission	60 days	11/07/19 08:00	02/10/19 17:00
Project Evaluation	1 day	03/10/19 08:00	03/10/19 17:00



Milestones:

All approvals in place – study ready to start	20/12/2018
Begin patient recruitment and data recording	10/01/2019
Last patient follow-up	17/04/2019

9.3 COSTS

Direct costs	
BIOPAC MP45 device and software	£2014
R and MATLAB software (free / license in-hand)	£0
Travel	£200
Contingency	£500
TOTAL Direct Costs:	£2714
Opportunity costs	
Clinical Engineer (Tristan Payne) 0.1 FTE 8a for 12 months	£6000
Statistician (Antonio Eleuteri) 8c for 1 week	£1600
TOTAL:	**£10,314**

All above direct and opportunity costs will be met by Medical Physics & Clinical Engineering, Royal Liverpool Hospital.

10 END OF STUDY

The study will formally end when the follow-up has been completed for the last participant. At the end of the study, a Project Evaluation will be carried out, as discussed in Section 8.13.

11 ARCHIVING

All appropriate documentation will be archived by the Chief Investigator and stored securely in Medical Physics & Clinical Engineering for a minimum of five years after the completion of the study. Anonymous participant data will be retained as set out in Section 8.4.

12 PUBLICATION POLICY

The results will be reported internally and used to decide if further research in the area is justified.

The results may be disseminated to the scientific community via an appropriate journal publication and/or a conference presentation, authored by the investigators and statistician, with acknowledgement given to any other people supporting the research at either site.

13 REFERENCES

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14 VERSION CONTROL

Version No.	Date Issued	Author(s)	Change Description
0.4	17/01/2018	AE	Added statistical and data analysis section. Added references.
0.5	18/01/2018	TP	Added full title, clarified data collected in Methods section, added section 8.15 Quality Plan, various minor changes
1.0	08/02/2018	TP	Added follow-up.
1.1	27/03/2018	TP	Added CPEO Exclusion Criterion (Section 4.3). Added inter electrode distance and impedance test meta data (Section 3.2). Refined Quality Plan (Section 8.15). Revised timescales

			(Section 9.2). Data archiving changed to minimum 5 years (Section 11).
1.2	02/05/2018	TP	Replaced Royal Liverpool Hospital with full RLBUHT name. Corrected Sponsor details (page 3). Corrected version control (Section 8.12)
1.3	02/05/2018	TP	Replaced indemnity with NHS indemnity (Section 8.5). Replaced sponsor as RLBUHT (Section 8.6 and 8.8).
1.4	10/05/2018	TP	Removed MREH as source of funding (page 1 and 2, Section 8.7). Study title revised to specify "data collection and analysis" instead of observational. Revised timescales (Section 9.2).
1.5	12/07/2018	TP	Minor clarifications to organisation and contact details; minor grammar corrections; Section 3.2, follow-up specified within four weeks; Section 8.11 added MREH PI as stakeholder; Section 8.12 added approval of amendments communication plan; Section 8.15 added Design Validation; Appendix 1 Section 15.1 revised Recording System diagram to include Buffer and replaced BSLCBL8 with SS2LB cable, PSU not removed from laptop before patient connection, system tested for electrical safety; Section 15.2.2 added stage to bypass buffer and isolate MP45 for impedance check; Section 8.4 reworded to clarify data protection, analysis and reference to new GDPR; Section 12 added internal report and conference presentation; Study Outcome Measures rewritten, Section 3.5; Consent, Section 8.3, reworded to clarify procedure and handling of consent withdrawal, 3 year data storage; Archiving Section 11 revised; title: EMG expanded; Introduction Section 1 rearranged for clarity; Objectives Section 2 rewritten to main plus secondary objective; Materials Section 3.1 updated with buffer; Ethics approval Section 8.2 corrected reference to anonymous data and added follow-up visit; Costs Section 9.3 minor correction; Personnel Section 3.4 reference to orthoptist in place of Ms Nichol; Inclusion Criteria Section 4.2 reference to Allergan removed.
1.6	25/07/2018	TP and AE	Minor changes; Method Section 3.2 clarified scoring; Statistics and Data Analysis Section 7 replaced binary class label with scoring and ordinal logistics regression model
1.7	06/09/2018	TP	Minor changes: removed reference to BOTOX®, replaced with BTX; Ethics Section 8.2 specified REC name; detailed procedure Section 15.2.2 revised to include Buffer Box ByPass following review of Risk Log.
1.8	21/11/2018	TP	Revised Timescales Section 9.2 to reflect progress to date and added milestones table.

15 APPENDICES

15.1 APPENDIX 1: EMG SIGNAL CAPTURE SYSTEM

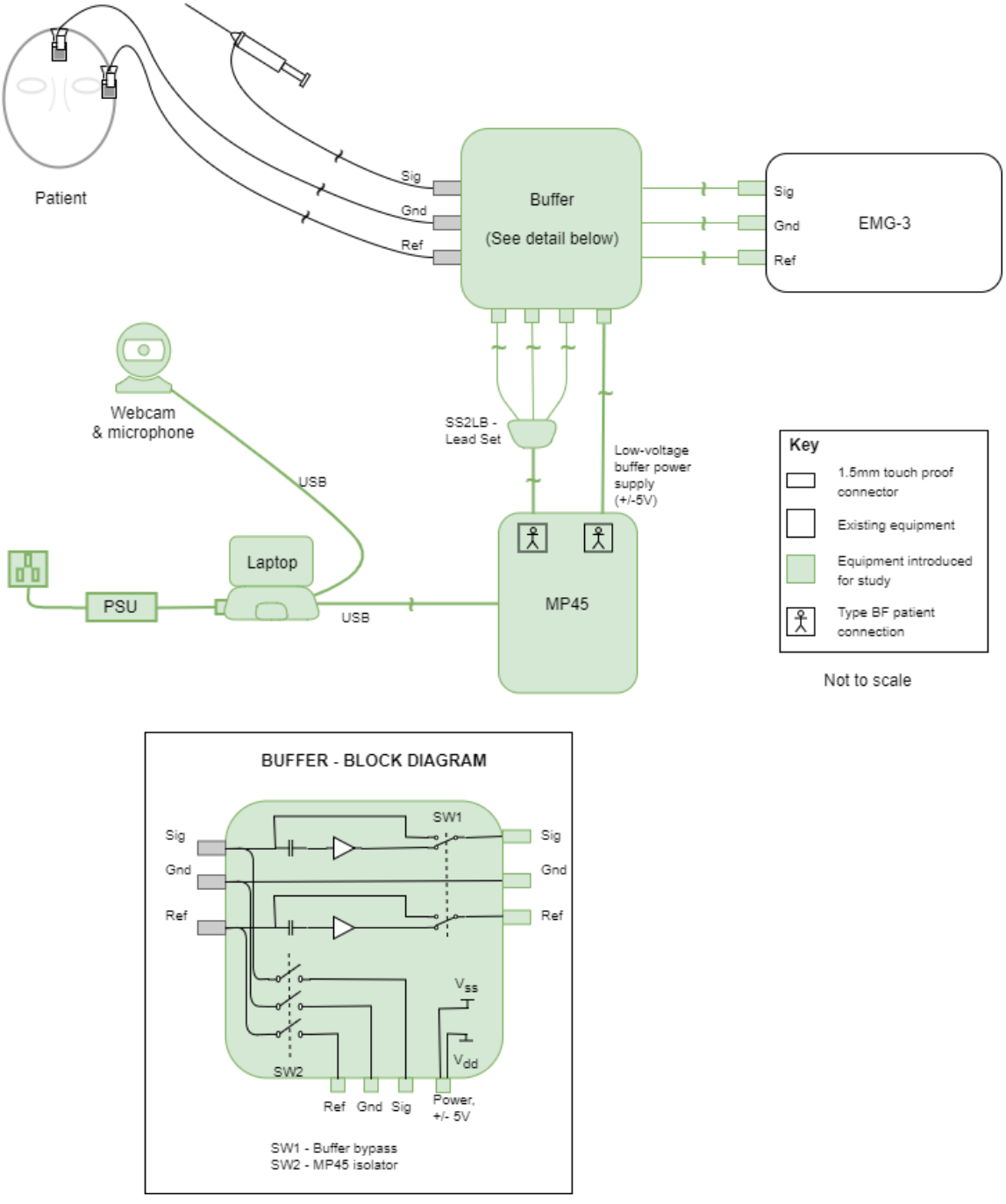

Figure 1 - EMG Signal Capture System Schematic

Equipment:

- EMG-3 is existing EMG monitor (Royal Liverpool Hospital, UK)
- SS2LB is input connection adapter (BIOPAC Systems, Inc., CA, USA)
- MP45 is 2 channel data acquisition device, USB powered (BIOPAC Systems, Inc., CA, USA)
- Buffer is custom made device (MPCE)
- Camera is standard webcam, e.g. HD 720P VIVEO (Trust International B.V., The Netherlands)
- Laptop is standard office laptop, e.g. B590 (Lenovo, Hong Kong)
- PSU is standard laptop mains adapter/charger for above laptop

NOTES:

- EMG-3 will be positioned on a trolley close to the patient's head as is current practice; the EMG Capture System (SS2LB, MP45, buffer and Laptop) will be located on the same trolley, or a second trolley positioned adjacent to the first.
- EMG cables are to be bundled (twisted/plaited/clipped) where possible, especially between EMG-3 and SS2LB, to reduce possibility of inducing additional noise.
- All cables are to be coiled where possible and the system cabling kept tidy to reduce the risk from slips or blunders.
- All recorded data will be stored in encrypted format, either on the laptop or on a memory stick.

SYSTEM SPECIFICATIONS ANALYSIS:

Specification	**Representative Requirement**	**EMG Signal Capture System**	**Outcome**
Electrical Safety	Meets or exceeds CE marked Medical Device standards	MP45 complies with IEC 60601-1 Medical Electrical Equipment General Requirements for Basic Safety and Essential Performance MP45 complies with IEC 60601-1-2 Medical electrical equipment. General requirements for basic safety and essential performance. Collateral Standard. Electromagnetic disturbances. Requirements and tests. MP45 is CE marked for compliance with the Low Voltage and Electromagnetic Compatibility directives. System tested for Electrical Safety to IEC 60601-1 standard	Requirement met
Input impedance	> 10 MOhm	SS2LB has input impedance of 11 MOhm (DC), 2 MOhm (differential) and 1 GOhm (a.c. 50 Hz)	Requirement met
Input voltage	> 10 uV	MP45 has input range adjustable from ± 200 µV to ± 2 V	Requirement met

Sampling frequency	> 10 kSps (samples per sec)	MP45 records max rate 48 kSps per channel	Requirement met
Input bandwidth	>5 kHz	MP45 provides adjustable lowpass filter, highest setting 8 kHz	Requirement met
Resolution	0.01 uV	MP45 digitises using 16 bit, resulting in resolution of 0.006 uV at 400uV p-p	Requirement met

15.2 APPENDIX 2: DETAILED METHOD

15.2.1 Preparation

Before the patient is moved into the clinical procedure room:

i. The EMG signal capture system is installed in the clinical room and connected to the EMG monitor.
ii. The researcher operating the EMG signal capture system ensures that EMG cables between the EMG monitor and the capture system are bundled together where possible to reduce induced interference;
iii. A brief test is carried out to verify the EMG signal capture system operates as expected;
iv. Anonymous details of the patient and treatment as set out in Section 3.2 are recorded at this point, or post-procedure.

15.2.2 EMG Signal Capture

After the patient is brought into the clinical procedure room:

i. The power supply from the MP45 to the Buffer Box is disconnected at the MP45; this is to reduce the chance of a falsely positive impedance test.
ii. The patient is prepared for treatment in the usual way, including connections to the EMG monitor and check of skin electrode impedance using the EMG-3 monitor while holding down the Bypass switch on the Buffer Box.
iii. The camera is positioned to capture the eye being treated only;
iv. The power supply from the MP45 to the Buffer Box is reconnected and the Bypass switch is confirmed to be released.
v. Prior to contact between the needle and the conjunctiva, the EMG signal capture system is triggered to begin recording EMG and the video/audio recording is started;
vi. During the procedure, the timing of events in Section 3.2 is recorded.
vii. The patient is disconnected from the recording system.

15.2.3 Post-Procedure

i. Information from the clinicians regarding the procedure and EMG signal heard is captured.