An investigation into an objective measure of muscle health: can electrical impedance myography measurements inform clinical decision making?

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Contents

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List of Tables, Figures and Abbreviations

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Abbreviations

ADL	Activities of daily living
ALS	Amyotrophic Lateral Sclerosis
AMG	Acceleromyography
BJR	British Journal of Radiology
BMI	Body mass index
C&VUHB	Cardiff and Vale University Health Board
CMG	Compressomyography
CT	Computed tomography
CTIMP	Clinical trials of investigational medicinal products
DXA	Dual energy x-ray absorptiometry
EIM	Electrical impedance myography
EMG	Electromyography
ESCI	Electrode skin surface impedance
FIT-HaNSA	Functional impairment test – hand and neck/shoulder/arm
HCPC	Health and Care Professions Council
HHD	Hand-held dynamometry
HRA	Health Research Authority
ICD	Internal cardiac defibrillator
ID	Isokinetic dynamometry
IPEM	Institute of Physics and Engineering in Medicine
IRAS	Integrated Research Application System
KMG	Kinemyography
MAS	Mobile arm support
MD	Muscular dystrophy
MMG	Mechanomyography
MMT	Manual muscle test
MND	Motor neurone disease
MPEC	Medical Physics and Engineering Conference

MS	Multiple sclerosis
NMB	Neuromuscular block
NSHCS	National School of Healthcare Science
PA	Phase angle
PMG	Posture and Mobility Group
PPE	Personal protective equipment
Q-Q	Quantile-quantile (plot)
R	Resistance
R&D	Research and Development
REC	Research Ethics Committee
REU	Rehabilitation Engineering Unit
RFM	Relative fat mass
SAM	Sponsorship assessment meeting
SCI	Spinal cord injury
SD	Standard Deviation
US	Ultrasound
X	Reactance
Xc	Capacitive reactance & reactance at the Characteristic Frequency
Z	Impedance
Zc	Impedance at the Characteristic Frequency

Abstract

Assessment of muscle health is important in many areas of health. The ability to objectively measure muscle health would provide scientific support for clinical decisions, for example in neurology when needing to differentiate between weakness and poor endurance. This work examines current measurement techniques and explores their objectivity and practicality in clinical and community settings. Active methods of measuring muscle health require the patient to activate or contract their muscles. Passive methods have the advantage of being applicable to a wider range of patients. Electrical impedance myography (EIM) was identified as an objective measurement technique that has the potential to inform muscle health in both the clinical and community setting.

Healthy volunteers were recruited into a single study group. The impedance of upper right limb, biceps brachii muscle, was measured when relaxed, and when activated using a multiple frequency bioimpedance meter (ImpediMed IMP^{TM} SFB7). Measurements of resistance and reactance enabled calculation of the impedance and phase angle.

Results and the literature indicate that EIM is easy to use and it was demonstrated to be an objective measurement technique. Paired t-test, $t = 4.56$, $p \leq 0.01$ indicated a significant difference in impedance between active and passive muscle in the small group (n=25) measured and a positive trend of age and increasing impedance was seen, Pearson correlation $r = 0.60$. A negative trend between age and phase angle was also observed, Pearson correlation $r = -0.68$. Trends in EIM measurements indicate a possible application to measurement of muscle degradation.

A larger clinical trial of healthy volunteers would help consolidate the findings presented here.

Lay Abstract

This project is about finding out how healthy muscles are. It looks at the ways in which muscles are measured now and then looks to see if there are any ways that don't need the patient to do anything. It looks at what might affect a measurement of muscle health, its strength or ability. The time of day may have an effect, a person may feel more energetic in the morning or the evening and perform better, they may have had a stressful time and not feel very confident, their mood may have an effect. If they have done a lot of exercise already, they may feel tired. This project aims to look for ways that make the measurement passive, like a blood test. If the test is influenced by the person being measured this may affect the treatment prescribed. Examples of widely used tests are the manual muscle test and grip tests. This project includes a clinical trial of electrical impedance myography (EIM) in which it is tested to see if the measurements are the same if the muscle is relaxed and if it has been activated by asking the person to tense their muscle. This is part of the investigation to try to find an objective measurement method. To be able to measure the muscle health without the patient needing to do something would make it more accurate.

Twenty-five healthy people took part in a trial to see if EIM measured on a relaxed muscle and on a contracted muscle was the same. The age of the 25 people was also recorded to see if there was a difference in EIM measured in older and younger people.

It was found that EIM in relaxed muscle and contracted muscle was different, but this is an important result too. EIM for older people was higher than for younger people in general. This may help with finding out how healthy a person's muscles are.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Dedication and Acknowledgements

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The Author

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- MHRA publications of medical device evaluations in the area of neonatal equipment (1998 to 2004),
- a BJR publication: Mutch SJ and Wentworth SDP. (2007) Imaging the neonate in the incubator: an investigation of the technical, radiological and nursing issues.
- Editing two IPEM Reports on medical device safety and design
    - Report 90: Safe Design, Construction and Modification of Electromedical Equipment. IPEM, York, 2004
    - Report 97: Guide to Electrical Safety Testing of Medical Equipment: the why and the how. IPEM, York, 2009
- Presentations and posters at national IPEM scientific meetings
    - MPEC 2004 – Should we use the x-ray tray
    - MPEC 2007 – light output from laryngoscopes
    - IPEM Scientific meeting 2008 – Wheelchair static stability
    - All Wales MPCE 2016 - A comparison of seating
    - All Wales MPCE 2021- Electrical impedance myography
- Presentations and posters at Posture and Mobility Group (PMG) conferences
    - Conference 2011 – wheelchair static stability
    - Conference 2018 – Pilot mobile arm support service
    - Conference 2019 – Safer for you, safer for us, caring for your wheelchair

The research work presented here has not yet been submitted to any scientific journal for publication.

1 Introduction and literature review

1.1 Rationale

The assessment of muscular function, health and ability is important in a diverse range of clinical disciplines from anaesthetics to physiotherapy. This project looks at the range of measurement techniques currently in use or development and considers their effectiveness and objectivity. It then investigates whether an objective measurement technique can be found or developed that can be used both in the clinical environment and the community setting. It will focus on the upper limbs.

Ability is defined as having the power or skill to perform or do something (Cambridge Dictionary, 2022), so the concept of muscle ability is defined as the means or skill in which voluntary movement can be achieved. It is often used synonymously with strength (Buckley et al., 1996; Gaskell, 2013). Ability is related to fine motor movements often needed in activities of daily living as well as full strength contractions of muscles such as those required for lifting heavy objects. The function of skeletal muscles is to provide the body with movement.

Muscle properties are usually defined as (Career and Technical Education (CTE), 2015):

Contractibility – ability to shorten; muscles can only contract or pull.

Excitability – ability to respond to a stimulus, either electrical or via a nerve or hormone.

Extensibility – ability to stretch.

Elasticity – ability to return to original length after stretching or contracting.

Adaptability – ability to change in response to how it is used, to enlarge or decrease depending on the work required.

All of these can be quantified but it is a complex process, and a measure of 'ability' is a function of, and relies on, all of these properties. Muscles can adduct (move a body part towards midline), abduct (move a body part away from midline), flex (decrease the angle at a joint), extend (increase the angle at a joint, or straighten) and rotate. These are all abilities and rely on the properties of the muscle.

This project developed from a need to assess arm muscles in patients who had been referred to Cardiff and Vale University Health Board (C&VUHB) Rehabilitation Engineering Unit (REU) for mechanical mobile arm supports (MAS) (Wentworth and Dube, 2018). MAS are designed to support arm weakness and are a device to assist activities of daily living (ADL). They can be used to assist feeding and drinking, using a keyboard or even turning the pages of a book. They can also be used in rehabilitation programmes and to assist in maintaining range of arm movement in patients at risk of contractures and other movement limiting conditions. In assessing the arm function of patients in their homes, it became apparent that manual muscle testing was not objective and was an inadequate outcome measure of success with a MAS; motivation for independence and good local support were better indicators. This raised the question of how muscle function could be measured objectively and reliably in all healthcare settings, including the patient's home.

1.2 Background

Analysis of upper arm movement and the forces involved has long been studied in biomechanics although it has tended to take second place to gait analysis (Buckley et al., 1996; Anglin and Wyss, 2000; Nordin and Frankel, 2012). A small search recorded in **Appendix 1** demonstrates this. **Appendix 2** provides a brief outline of kinesiology, biomechanics and kinematics and raises some of the ongoing queries, for example whether or not there is a standardised scale for clinical movement:

Anglin and Wyss (2000, p.542) discuss how there are no standard activities in comparison to gait and that none, at that point in time, could be recommended. Veeger and Nikooyan (2011) produced an online interactive document to share practice on shoulder measurement protocols demonstrating that there was no agreed practice at that time. However, the functional impairment test – hand and neck/shoulder/arm (FIT-HaNSA) test (Kumpta et al., 2011; Hawkes et al., 2011) has been demonstrated to be reliable for upper body measurements.

Leaving aside clinical motion measurement, and concentrating on the muscles used for the motion, it has become apparent that there are many inconsistencies in measuring muscle ability, function, force and health because of the complexity of the process of muscles moving the body (Buckley et al., 1996; Merlini, 2010). As described in **Appendix 2**, which outlines biomechanics, the biochemical process of powering the muscle is highly complex and the rate at which the energy is used defines the fatiguability of the muscles. The actual muscle fibres are grouped into motor units activated by a single motor neurone and are either at rest, in the process of contraction or fully contracted; they cannot be sustained or rendered into a state of partial contraction. This gives a ‘digital’ feel to muscle contraction. However, the motor units are not discretely aligned and contiguous, but are interspersed making the arrangement much more complex to unravel but providing a more effective system for muscle action and sharing of the required force workload. Motor units may also consist of only a few muscle fibres (Nordin and Frankel, 2012), allowing very fine muscle control such as around the eyes, or they may consist of thousands of muscle fibres such as in the large motion muscles of the legs. All of these factors complicate muscle activity measurement.

1.3 Aim and objectives

From this background this review explores what can be measured; the problems of measurement and its objectivity. The aim is to investigate whether there is a method of measuring muscle health, function and ability that can be used objectively in the clinical environment or the community with equal ease or whether such a method can be developed.

1.4 Muscle testing

Research on muscle testing is considered and the relevance to the current study critically evaluated.

1.4.1 Manual muscle testing

Manual muscle testing is widespread in healthcare (Brooke et al., 1981; Bohannon, 1987; Noreau and Vachon, 1998; Kirschner et al., 2010; Hawkes et al., 2011; Peek, 2014). It is widely used in physiotherapy and occupational therapy for assessing patients' muscle function and ability and its reliability and repeatability has also been evaluated (Frese et al., 1987; Mahony et al., 2009; Gaskell, 2013, p.213; Physiotutors, 2015; Physiopedia, 2019). Bohannon's (1987) review describes in detail mechanical strength testing and aspects of the instruments used, the clinician's scale and effect as well as psychological effects. The psychological effects include the possibility of patients consciously or unconsciously modifying their ability to perform the test depending upon their mood, motivation and mental state at the time of testing. Gaskell (2013) also discusses this to help physiotherapists be aware of the influence of patient psychology. There is also the subjective nature of the observer. This may take the form of the physical strength of the assessor or their training and also their observation muscle test results. Physiopedia (2021) describes the manual muscle test.

Bohannon (1987) uses as the definition of strength: the ‘capacity of a muscle or group of muscles to bring force to bear on the environment’ and chooses four criteria that muscle strength measurements must fulfil in order to be meaningful:

- They must be sensitive enough to distinguish sub-normal from normal muscle strength.
- They should be precise enough to document both increases and decreases in strength.
- They should be reliable.
- They should be predictive of other variables of potentially greater importance.

The objectivity of the measurement is clearly in Bohannon’s (1987) thoughts although not stated as one of the criteria. The criteria may provide an important basis for a tool to test the quality and objectivity of techniques to measure muscle ability. The prediction of other variables may relate the measurements to physiological changes indicating underlying pathology. For example, decreasing muscle strength objectively measured could be linked to neurological disease such as motor neurone disease (MND), amyotrophic lateral sclerosis (ALS), muscular dystrophy (MD), or multiple sclerosis (MS); whereas an increase in muscle strength over time could indicate effective rehabilitation following a stroke, for example.

1.4.2 Comparing mechanical muscle testing and manual muscle testing

Noreau and Vachon (1998); Mahony et al., (2009); Abizanda et al., (2012); Peek (2014) compare different mechanical muscle testing methods. Noreau and Vachon (1998) compare three methods of mechanical muscle strength testing: Manual muscle testing (MMT), myometry using a hand-held dynamometer and isokinetic dynamometry (ID), which was considered the ‘gold standard’ at that time, (see **Table**

1.1). They realistically consider the advantages and disadvantages of each type of testing in their comparative study on patients with spinal cord injury (SCI). They conclude that in monitoring rehabilitation manual muscle testing (MMT) is not sufficiently sensitive especially at higher strengths; myometry and isokinetic dynamometry give more consistent results and are useful in monitoring rehabilitation. Isokinetic dynamometry is however, expensive, and not suitable for in-the-field measurements; it requires expensive heavy equipment that is not easy to transport or set up in a home environment. Frese et al., (1987) conclude that using MMT to make accurate clinical assessment 'of patient status is of questionable value'; but Mahoney et al., (2009) find that in children with spina bifida hand held dynamometry (HHD) is appropriate when they have sufficient strength but if not then MMT is appropriate. No work has been found where there is testing in a variety of patient groups. This may be due to the complexity of the area of study and muscle testing across a variety of neuromuscular conditions may not be consistent, for example MMT and HHD may be reliable in spina bifida but not in muscular dystrophy or amyotrophic lateral sclerosis (ALS).

The equipment required for muscle testing is perhaps a factor when considering the NHS vision of more health services being delivered at home (NHS Wales, 2018, p.8; NHS, 2019, p.12) and also the aims of this project to develop a means of muscle testing which can be used in the clinic and in the community with equal ease. Noreau and Vachon's (1998) study of testing in SCI rehabilitation is highly relevant to this study which was initiated from assessment of patients with a neurological condition which was unlikely to improve; however, a testing technique is sought here that is applicable to all patient groups.

Peek's (2014) systematic review of muscle strength clinimetrics provides an in-depth study of manual muscle testing (MMT), hand held dynamometry (HHD) and isokinetic dynamometry (ID) again in spinal cord injury (SCI) patients. She concludes that the literature supports wider use of HHD over MMT and ID. She also makes the very important point that measurement should not be taken for measurements' sake but for the direct benefit of the patient (Peek, 2014, p.71). Peek (2014) also offers good support for Bohannon's (1987) four criteria of muscle measurements.

The techniques described cannot be said to be highly objective since they depend on the patients' response and the clinician's skill in quantifying muscle ability. Their effectiveness has been studied and been found to be acceptable but not highly sensitive to subtle changes (Frese et al., 1987; Noreau and Vachon, 1998; Mahoney et al., 2009).

1.4.3 Electrical and other methods of muscle testing

Other methods of muscle testing are based on electronically detecting the physiological nature of muscle action: neuromuscular signals, the acceleration, electrical properties or vibration of the muscle (Engbaek et al., 1994; Hemmerling et al., 2000; Trager et al., 2006; Roberts and Gabaldon, 2008; Rutkove, 2009; Brull and Murphy, 2010; Hawkes et al., 2011; Schepens and Cammu, 2014; Vilaca et al., 2014; Fortier et al., 2015; Lee et al., 2015; Colegrave et al., 2016; Naguib et al., 2017; Murphy, 2018). Some include imaging techniques to better understand the structure or changes in muscle architecture (Goodpaster et al., 2006).

Hawkes et al., (2011) investigated a validated upper limb test, the functional impairment test – hand and neck/shoulder/arm (FIT-HaNSA), (MacDermid et al., 2007)) in conjunction with electromyography (EMG) measurements and

demonstrated that a wider range of muscles are involved in upper limb activities for daily living (ADL) than was previously considered.

The use of electromyography (EMG) in studying movement, and in particular ADL after stroke (Roy et al., 2009; Lowe and Olaighin, 2014; Lee et al., 2015), are well described and may be used as a resource for this study. An example is Lee et al.'s, (2015) study of EMG in patients with chronic stroke during the action of drinking from a glass. A comparison with healthy people would be informative. Consistent ADL lend themselves to measurement and patient needs.

Investigations of older adults' (Goodpaster et al., 2006; Vilaca et al., 2014) muscle mass and strength using a combination of dual energy x-ray absorptiometry (DXA), computed tomography (CT) and ID yield interesting conclusions. Goodpaster et al., (2006) concludes that although both muscle mass and muscle strength decline in older adults the decline in strength was greater than the decline in mass indicating a decline in the quality of muscle, where quality is defined as a function of muscle mass and strength (Musclesound, 2018). Keller and Engelhardt (2013) also found evidence for muscle mass and strength loss in older adults. Vilaca et al., (2014) conclude that increased body fat has a negative effect on muscle quality. These are important considerations when looking at the measurement of muscle quality. Older adults may also be an important patient group on which to test an objective measure.

These studies lead to the question of what is the link between neuromuscular health and the ability of muscles to function. Muscle ability is used instead of strength as described in **Section 1.1**. It has been described as a function of defined muscle properties and it is considered here as a more practical term relating to physical, real-world use of muscles. Active neuromuscular function indicates that the muscle responds to the neural signal. As already described, care must be taken in

interpretation of electromyography (EMG) and muscle movement. EMG reflects the electrical, not mechanical, events in muscle contraction (Roberts and Gabaldon, 2008, p.312). EMG measurements are more objective since they cannot be influenced by the patient except in responding to requests for muscle action, and often needle electrodes are used to obtain the most reliable data. EMG measurements are well-established and effective indicators of neuromuscular health. They are, however, sensitive to electrode positioning and other electrical devices. They are used extensively in gait studies.

1.4.4 Passive muscle testing

The ability to test muscles passively holds the advantage of being more objective than manual muscle testing (MMT), muscle testing manually with a mechanical device or using EMG. Muscle testing during and in reversal of anaesthesia has been explored in relation to recovery. Objective monitoring of anaesthetic recovery is advocated to improve patient safety (Engbaek et al., 1994; Hemmerling et al., 2000; Claudius and Viby-Mogensen, 2008; Liang et al., 2013; Sakai et al., 2015; Dutu et al., 2018).

Sakai et al., (2015), compared acceleromyography (AMG) and electromyography (EMG) during neuromuscular block (NMB) and found that acceleromyography consistently showed recovery from NMB when EMG did not. Acceleromyography measures an acceleration in the muscle, a mechanical force, whereas EMG measures an electrical force. Sakai et al.'s, (2015) comparison showed clearly that the two measurements are not synchronous and cannot be used interchangeably. They explain that their results indicate that the muscle becomes mechanically active while the NMB has not completely cleared, and this is important in measuring muscle activity. It implies that EMG measurements must be used with care when physical

and mechanical muscle action are being investigated. When thought through this is a logical conclusion since electromyography (EMG) is measuring electrical activity at the motor neurone and not the actual force effect.

1.4.5 Comparison of muscle measuring techniques

Dutu et al., (2018) reviewed the use and methods of neuromuscular monitoring during and after anaesthesia. Their aim was to encourage greater consistency of monitoring to provide more effective patient care. Their findings are relevant and can be applied to this study particularly because in their review their patients are not responsive, or only barely responsive so monitoring of their neuromuscular response must be objectively dependent on the clinical staff and measurement technique. The challenges lie in the type of measurement and in understanding what it is actually measuring.

Table 1.1 summarises the understanding of neuromuscular measuring techniques, with additions to include muscle testing techniques described in **Sections 1.4.1, 1.4.2, 1.4.3 and 1.4.4**. It is based on Dutu et al., (2018, p.56) and is augmented with additional information.

Table 1.1 Techniques used for quantitative neuromuscular monitoring

Monitoring technique	Description	Devices for clinical use	Advantages	Limitations
Mechanomyography (MMG)	Measurement of the evoked mechanical response of the (adductor pollicis muscle) APM following ulnar nerve stimulation.	None	Precise Reproducible Gold standard	Cumbersome setup (Murphy, 2018)
Electromyography (EMG)	Measurement of the muscle action potential following nerve stimulation.	Datex-Ohmeda (neuromuscular Transmission) NMT ElectroSensor	Best indicator of pure neuromuscular function (Naguib,et al., 2017). Comparable with MMG but more consistent in time (Engbæk et al., 1994; Brull and Murphy, 2010). Available for many sites (Hemmerling et al., 2000). Free muscle movement not required.	Influenced by other electronic devices in the OR (diathermy) or local temperature (Murphy, 2018; Brull and Murphy, 2010).
Acceleromyography (AMG) Most widely used technique, the de facto standard of clinical care in anaesthesia [Rodney et al., 2015; Naguib et al., 2017).	Measurement of the acceleration of the stimulated muscle with a piezoelectric sensor.	**Classic AMG:** (Train of four) TOF-Watch InfinityTrident NMT (neuromuscular transmission) Pod **3D AMG:** STIMPOD TOFscan (Murphy, 2018)	Easy to handle. Suitable for any free-moving muscle (Fortier et al., 2015). 3D transducer to measure more precisely the muscle movement (Colegrave et al., 2016)	Not interchangeable with electromyography/mechanomyography TOFR (train of four ratio) overestimation by at least 0.15 (Claudius and Viby-Mogensen, 2008; Liang et al., 2013) Baseline TOFR > 1.0 (Suzuki et al., 2006).
Kinemyography (KMG)	Measurement of the electrical signal generated by the bending of a piezoelectric sensor strip placed between the thumb and the index.	Datex-Ohmeda neuromuscular transmission MechanoSensor	Easy to use	Available only for the ulnar nerve – adductor pollicis muscle (APM) group. Free thumb movement required. Good strip placement between the fingers required (Naguib et al., 2017).

Monitoring technique	Description	Devices for clinical use	Advantages	Limitations
Phonomyography	Measurement of the low-frequency sounds evoked by muscle contraction	None	Easy to apply. Usable for many sites (Murphy, 2018). Good correlation with acceleromyography, electromyography, mechanomyography (Trager et al., 2006).	
Compressomyography (CMG)	Modified non-invasive blood pressure cuff measuring the block depth by brachial plexus stimulation through electrodes attached on its inner surface (Schepens and Cammu, 2014)	TOF-Cuff	No need for free arm movement	Not interchangeable with MMG, but a TOF-Cuff® TOFR > 0.9 correlates well with a MMG TOFR > 0.7 (Veiga et al., 2017)
Manual Muscle Testing (MMT)	Clinician uses own body to grade muscle activity and function.	None	Can be used anywhere, clinic or community	Reliability (Mahoney et al., 2009; Frese et al., 1987). Sensitivity. Patient / clinician influence/ psychology
Hand Held Dynamometry (HHD) (Noreau and Vachon, 1998; Abizanda et al., 2012)	Device to measure grip force	Hand held dynamometer eg JAMAR	Portable, widely available, inexpensive	Reliability, sensitivity. Patient influence / psychology
DXA (Dual-energy x-ray absorbiometry) (Goodpaster et al., 2006)	Device used to measure bone density	Established DXA machines eg Hologic QDR 4500	Accurate	Radiation dose Expensive Not portable
Computed tomography (CT) (Goodpaster et al., 2006)	Body scanning device	Established CT scanners	Accurate, reliable	Radiation dose Expensive Not portable

Monitoring technique	Description	Devices for clinical use	Advantages	Limitations
Electrical Impedance Myography (EIM) (Rutkove, 2009; Rutkove et al., 2012; 2013; 2014; 2017; 2018; Sanchez and Rutkove, 2017; Sanchez et al., 2016; 2017)	Device is passive and measures the reactance and impedance of muscle in a range of frequencies	Myolex ImpediMed IMP^{TM} SFB7 Skulpt	Used in body composition studies. Has been demonstrated as an effective biomarker in clinical trials (Rutkove et al., 2012; Rutkove et al., 2014)	Expensive Still experimental Sensitive to electrode location

Dutu et al., (2018) do not consider electrical impedance myography (EIM), perhaps because it has generally been used in active studies. Successful application of EIM to neuromuscular studies has developed over the last 10 years (Rutkove, 2009; Rutkove et al., 2012; Rutkove and Darras, 2013; Rutkove et al., 2014; L. Li et al., 2016a; 2016b; X. Li et al., 2017; Z. Li et al., 2017; Rutkove et al., 2017; Sanchez et al., 2016; 2017; Sanchez and Rutkove, 2017; Rutkove and Sanchez, 2018; Cebrian-Ponce et al., 2021). X. Li et al., (2017) demonstrate successful application of EIM in relation to muscle resistance before and after a botulinum toxin injection. Although they acknowledge that EIM is sensitive to a change they are not detecting a change in muscle property since the measurements are carried out too soon after injection. They realise the potential of EIM even though botulinum toxin is thought to generally reach maximal effect after 48 hours. Bartels et al., (2015) successfully used multifrequency EIM to assess skeletal muscles.

Rutkove (2009) and Sanchez and Rutkove (2017) describe the mechanism and theory of EIM and in subsequent work test the effectiveness in neuromuscular conditions, demonstrating its effectiveness as a clinical biomarker (Rutkove et al., 2012; 2014). EIM's use as a biomarker in motor neurone disease (MND) is also recognised by Turner et al., (2013); they also describe as an advantage EIM's ability to be used in any accessible muscle and in their case the ones deteriorating most quickly. This is strong evidence for the effectiveness of EIM and indicates its objectivity.

However, care must be taken in searching for correctly described techniques; one example found is Bauza and Lachtara (2016). Their project title includes the words electrical impedance myography, but their method describes the use of electromyography (EMG).

Z. Li et al., (2017, p.1576) investigated the structure of the electrical impedance myography (EIM) electrode shape in a study on carpel tunnel syndrome and provides a very useful insight into the actual surface structure of the electrode. They demonstrate that a microholed or micropillared surface with saline reduces the electrode-skin surface impedance (ESCI) to less than that achieved using a commercial Ag/AgCl adhesive electrode at all frequencies but especially below 100Hz. Z. Li et al., (2017) go on to describe the challenges of using EIM: it is a new technique and more work on electrodes is needed. They see a need for computer modelling to mitigate the effects of the impedance of subcutaneous fat and also recognise that most research has been done on passive muscles and they look for more work to be done in real time on contracting muscles, which is a very interesting concept. L. Li et al., (2016b) present results for passive and active muscles which indicates only a small difference in EIM between active and passive muscles. This reinforces the statements from Turner et al., (2013) regarding the advantage of EIM measuring effectively on many different muscles and not being constrained to specific muscle groups. Work has been done using EIM on the tongue which is a significant area in motor neurone disease (MND) (Pacheck et al., 2015; Mcilduff et al., 2017).

For more details please see **Appendix 3** which covers the physics and background of electrical impedance myography.

1.5 Controversies, problems and unanswered questions

Current methods of assessing muscle health, quality and ability in the clinical or home environment are not objective. Manual muscle testing using the Oxford Scale (Frese et al., 1987; Gaskell, 2013) or a similar scale relies on the co-operation of the patient as well as the skill, strength, and experience of the clinician in assessing

muscle consistently. The impact of the psychological state of the patient is also important. Laboratory and research methods of assessing muscles rely on expensive or heavy technology and have been shown to provide more objective measurement, however, many still rely on patient compliance and co-operation. In any testing reliant on co-operation there will be a psychological input from both the clinician and the patient whether conscious or unconscious and this reduces the reliability and objectivity of the test.

Electromyography (EMG) measures muscle activation but not strength, force, or actual ability (Sakai et al., 2015; Naguib et al., 2017). It is influenced by other electrical signals and is sensitive to measuring position. Muscle mass is not an indication of ability (Goodpaster et al., 2006; Vilaca et al., 2014). Mechanomyography (MMG) is called the 'gold standard' (Murphy, 2018), but is difficult to measure and can only currently be measured in the laboratory or in a well-appointed clinic or theatre. Electrical impedance myography (EIM) has been investigated over the last 10 years and is moving slowly out of the laboratory and into clinical practice. More investigation as to what it is actually measuring is needed and it is also sensitive to electrode position. It has been cited as a reliable biomarker for amyotrophic lateral sclerosis (ALS) studies (Turner et al., 2013; Rutkove et al., 2012; 2014). It has been used in multiple sclerosis (MS) and muscular dystrophy (MD) studies and its strength appears to lie in its ability to provide information on the passive electrical properties of muscles. It has also been used in studies of sarcopenia (Keller and Engelhart, 2013; Uemura et al., 2020). This makes it more applicable as an objective measure.

Cuthbert and Goodheart (2007) discuss identifying a 'gold standard' test for muscle function but do not find one. Dutu et al., (2018) classify mechanomyography as a

‘gold standard’ measure but this is from an anaesthetic perspective; they also describe it as having a cumbersome setup.

1.6 Hypotheses, aims and objectives

Some work has been done (L. Li, et al., 2016b) on electrical impedance myography (EIM) measurements in passive and active muscle in young adults. This showed that there were no significant changes in the measured reactance of the impedance measurements in contracted and fatigued muscle, implying that passive muscle would be little different.

The aim of this work is to investigate an objective measure of muscle function, activity, and ability. From the literature EIM appears to be a viable measurement technique. It is a passive measurement which makes it more objective since it is less likely to be influenced consciously or unconsciously by clinicians or patients. This work plans to test EIM in passive and active muscles and discuss whether EIM may meet the objective. Measurements will be made on adult volunteers of ages between young adulthood and old age. It is hypothesised that testing muscle in adults in a wide age range may inform which applications can be used for diseased muscle based on research work on sarcopenia. Due to time and resource constraints only a small feasibility study will be possible.

The research question: Can electrical impedance measurements of muscles be used to assess muscle health? This will be explored using the following hypotheses:

- The impedance of passive and active muscle is the same.
- The impedance phase angle of passive and active muscle is the same.
- The impedance of muscle varies with age.
- The impedance phase angle of muscle varies with age.

The variation of impedance and phase angle may be investigated over a wide age range and also using age groups. A ‘cut-off’ age as described by Keller and Engelhart (2013) and age range groups, as described by Uemura et al., (2020), may reveal otherwise hidden trends in a small study.

1.7 Relevance and value

This research work aims to inform clinical muscle testing and investigates finding an objective measure of muscle health, looking to link it to muscle ability and function. It seeks to validate the use of electrical impedance myography (EIM) as a measurement tool which could be used clinically in healthcare venues and in the community. This work seeks to make muscle assessment measurements more scientifically reliable.

A method of measuring muscle health, function and ability objectively which is not influenced by the patient or clinician would improve the scientific validity of muscle measurements.

A method of measuring muscle function in patients who are not able to co-operate, either through muscle disease or mental capacity, would improve the equality and increase the range of patients who could be supported and treated.

2 Methodology

2.1 Introduction

As discussed in the introduction and the literature review this research was carried out with the aim of investigating an objective measure of muscle quality, function and ability. The measurement method seeks to quantify muscle properties without requiring active participation by the person being measured, thereby increasing objectivity both on the part of the person making the clinical measurement and on the part of the person being measured. Consideration was given to the objectivity and the practicality of available testing methods. One method discussed above was the use of electrical impedance myography (EIM) and it was using this method that measurements were made. The research question and hypotheses as stated above were tested and a clinical trial (a non-Clinical Trials of Investigational Medicinal Products (non-CTIMPS)) was proposed. **Appendix 4** provides details of the clinical trial documentation, including the proposal, the sponsorship request form, the clinical trial protocol, the participant information sheet, the informed consent form, the volunteer poster, the data collection sheet and certificate evidence of training in Good Clinical Practice (GCP) accredited by the National Institute for Health Research (NIHR).

A proposal was presented to and accepted by the University of Manchester (see **Appendix 4.1**) for this study. Sponsorship was sought from Cardiff and Vale University Local Health Board (C&VUHB) via the Research and Development (R&D) Department (See **Appendix 4.2**). This involved scrutiny, agreement by the Directorate R&D Lead, a sponsorship assessment meeting (SAM) with the C&VUHB R&D Lead and following a small amendment, which requested the study to exclude participants with active arthritis, it was passed and was accepted. The next stage

was submission of an Integrated Research Application System (IRAS) form, including the registration of the clinical trial with a database. The Health Research Authority (HRA) and Research Ethics Committee (REC) then needed to assess the IRAS form and this was successfully completed and approved (reference: 20/YH/0055). The forms were handled by the Cardiff and Vale UHB R&D Department and I was not required to attend the Research Ethic Committee which was the Yorkshire and The Humber – South Yorkshire Research Ethics Committee, based in Newcastle upon Tyne.

With the trial approved, recruitment of healthy volunteers could begin. However, at this point the COVID-19 pandemic was declared and all non-COVID-19 research projects were put on-hold. This caused a delay, and no participants could be recruited until the hold was released.

2.2 Research and Development Approval and Ethical Approval

Ethical approval (REC 20/YH/0055) was received following submission of the research proposal to Cardiff and Vale University Local Health Board (C&VUHB) Research and Development Department (R&D). C&VUHB R&D agreed sponsorship, reference number 7703, and the research was submitted on an IRAS form, number 266115.

2.3 Participants

Healthy volunteers were recruited from fellow staff members, friends and family via a poster (version 1.1), see **Appendix A4.6**. Potential participants contacted the Chief Investigator and were provided with Participant Information Sheet (PIS) (Version 1.2) see **Appendix A4.4**. They were given at least 48 hours to study this and the opportunity to contact the researcher and ask any questions.

Inclusion criteria for the study were:

- Over 18 years old.
- No existing neurological condition.
- No active arthritis.
- Not pregnant.
- No heart disease.
- No internal electrical device (pacemaker or internal cardiac defibrillator (ICD) or other).
- Able to give informed consent.

A single test visit was arranged. At that visit potential participants were asked whether they had read the Participant Information Sheet and whether they had any questions. Their eligibility was checked to ensure that they met the inclusion criteria and they were asked if they were happy to proceed. They were also asked not to drink anything for an hour before the measurements and to ensure their bladders were empty. Participants were also asked whether resting their arm on the horizontal surface and then activating their biceps would cause them any pain. They were also asked not to carry out intensive exercise, for example running or going to the gym, for an hour prior to measurement. This was because increased fluid intake or exercise may affect the measurements (Sanchez et al., 2021). Participants completed a Consent Form (version 1.0, see **Appendix 4.5**), indicating their informed consent to take part.

Following the approved Protocol (version 1.1, see **Appendix 4.3**), a confirmatory explanation of the experimental measurements was given. Eligibility criteria and

measurements made were recorded on the Data Collection Sheet (Version 1.0, see **Appendix 4.7**).

The COVID-19 pandemic required that extra precautions were taken, and Personal Protective Equipment (PPE) worn at participant visits. Participants wore disposable surgical masks, the Chief Investigator wore a disposable surgical mask, disposable apron and disposable gloves. Decontamination of equipment precautions were also very carefully followed and extra time between measurements of different participants allowed. Measurements were carried out in four safe locations; primary considerations were space for social distancing and ease of cleaning surfaces and equipment used.

Participant height, weight and waist measurement were recorded to the nearest 0.5cm, 0.1kg and 0.5cm, respectively. Participant age, in years, was also recorded. A Marsden M-545 professional medical scales (Class III device Marsden Ltd, Rotherham, UK) was used for weight measurement. A Seca 213 portable Stadiometer (Seca Deutschland, Hamburg, Germany) was used for height measurements. A pocket tape measure was used for waist measurements. Participant height and weight were measured without shoes on. Waist measurements were made over one layer of clothing.

Impedance was measured using an ImpediMed IMP^{TM} SFB7 single channel, tetrapolar bioimpedance device (ImpediMed Ltd, Pinkenba, Qld, Australia), see **Figure 2.1**.

Calibration of the IMP^{TM} SFB7 was carried out as per the manufacturer's instructions. At all times it passed the self-calibration process.

Adhesive dual tab electrodes (Lymphedema, Dual Tab Electrode, Medimark Europe, Grenoble, France) as specified by ImpediMed (Pinkenba, Qld, Australia), see **Figure 2.2**, were used. These were attached to the participant's right biceps brachii as shown in **Figure 2.3**.

Figure 2.1 IMP^{TM} SFB7 with colour coded leads and unused adhesive electrodes

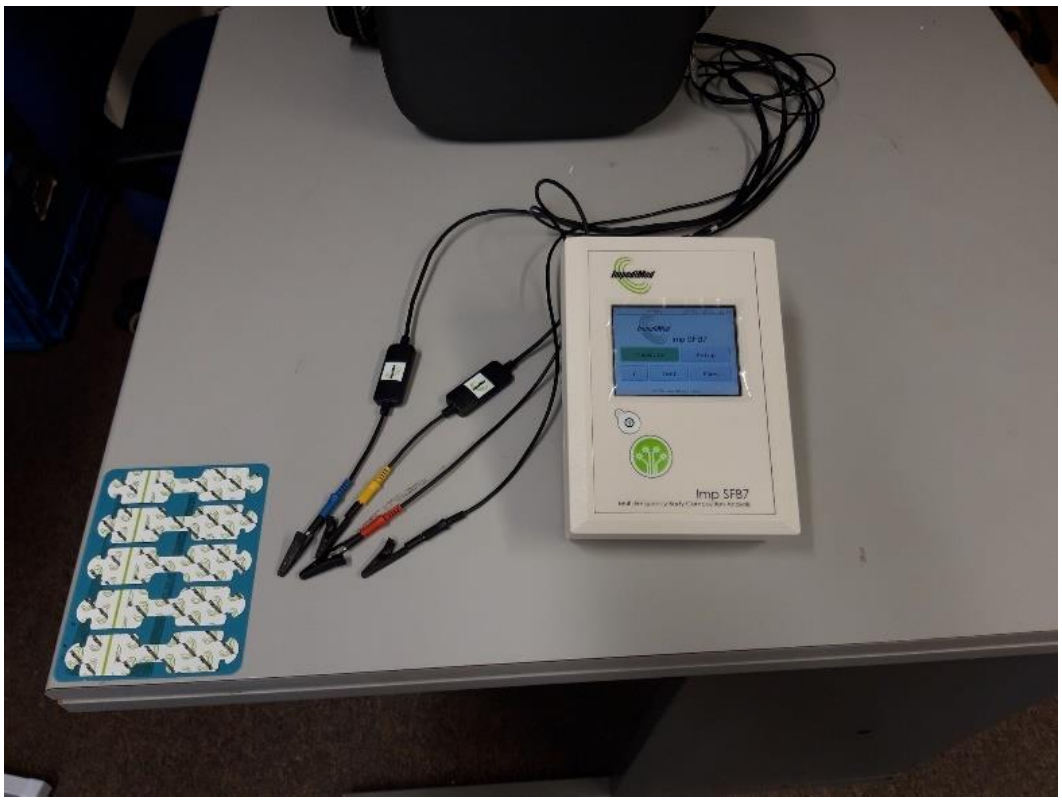
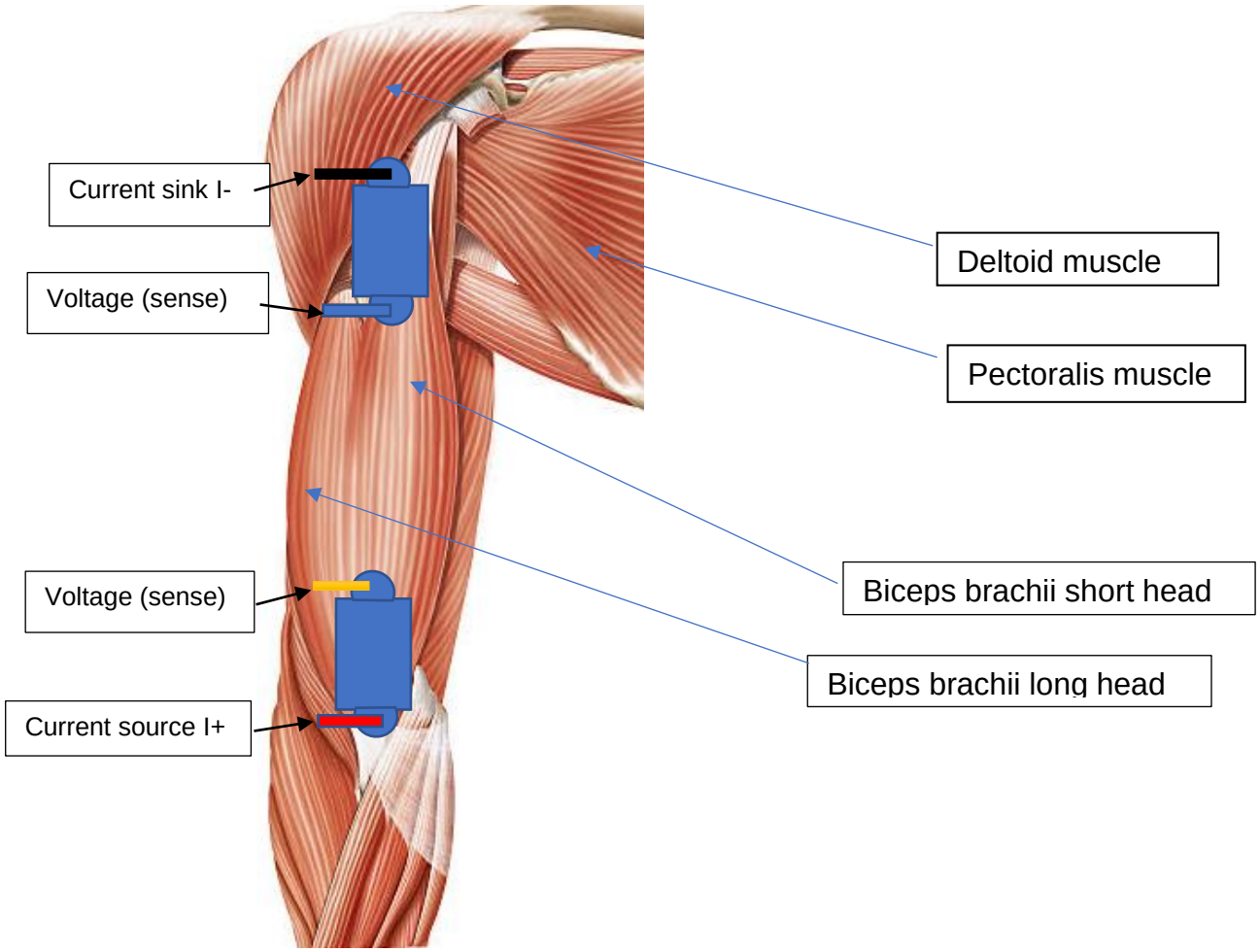


Figure 2.2 Adhesive dual tab electrodes

Figure 2.3 Right biceps brachii with electrode placement

Based on Image from https:// images.fineartamerica.com. 1-muscles-of-right-upper-arm-asklepios-medical-atlas.jpg (675×900) (fineartamerica.com) Black and red electrode connections are the current source and sink leads. Blue and Yellow electrode connections are the voltage sensing leads



The location of the dual tab electrodes was determined by the palpation of the partially active biceps. For the upper arm location, the short head of the biceps was chosen as this was the most consistent point to find on the participants. The participant was then asked to relax and the leads from the IMP^{TM} SFB7 were attached to the electrodes: current sink (black) to the proximal tab on the dual electrode at the top of the arm, sense (blue) next to it on the same dual electrode, sense (yellow) on the upper tab of the lower dual electrode and current source (red)

on the lower tab of the distal dual electrode. This was as per guidelines from ImpediMed for the IMP^{TM} SFB7 segment measurement protocol and adapted for the biceps instead of the whole arm, see **Figure 2.3**. The circumferences were not measured since the extra cellular water volume was not required.

Four sets of electrical impedance myography (EIM) measurements were taken for each participant. As per the protocol the participant was asked to sit and relax with their lower right arm resting horizontally on a support surface for a minimum of five minutes. Arm dominance was not checked, and measurements were made on each participant's right arm. After five minutes 10 sets of readings were taken at 256 discrete frequencies in the range 5kHz to 500kHz. In each set of measurements impedance, Z, reactance, X, resistance, R and phase angle, PA, were measured at each frequency. The participant was then asked to make a fist and flex their arm while leaving their elbow on the horizontal surface. They were asked not to try for maximum force but to flex their biceps enough to be sure it was activated. A further 10 sets of readings were taken.

The participant was then asked to relax their arm again for a minimum of five minutes and the procedure above repeated, constituting two cycles of measurements.

After the measurements the participants were asked if they felt any sensation during the measurements. This was asked afterwards to ensure there was no suggested effect. It was not expected that any of the participants would feel any sensation during the measurements since the current is very low: 200μA AC RMS (IMP^{TM} SFB7). The electrodes were then removed from the participants, and they were also asked to rest for a few minutes before leaving.

Measurements were downloaded to a laptop using the 'upload' protocol from the ImpediMed IMP^{TM} SFB7 and stored. Each file was exported to Microsoft Excel (2019) for later analysis.

After measurement the electrodes were disposed of and the leads and meter cleaned with Clinell wipes. During measurement the assessor wore a surgical face mask and disposable gloves.

2.4 Principles of electrical impedance myography

The impedance across biological tissue is often referred to as bioimpedance and it refers to the electrical properties of the tissue when a current flows through it (Holder 2004). Impedance varies with frequency and has been found to be sensitive to tissue type and histology. Please see **Appendix 3** for the physics and principles of electrical impedance myography as applied to biological tissue.

Impedance (Z) = Resistance (R) + Reactance j(Xc) **Equation 1**

Where j indicates an imaginary number symbolising the complexity.

$$Xc = \frac{1}{2\pi fc} \quad \textbf{Equation 2}$$

$$R = \frac{V}{I} \quad \textbf{Equation 3}$$

Where f= frequency (Hz), c= capacitance (farads) V= voltage (volts) and I = current (amps).

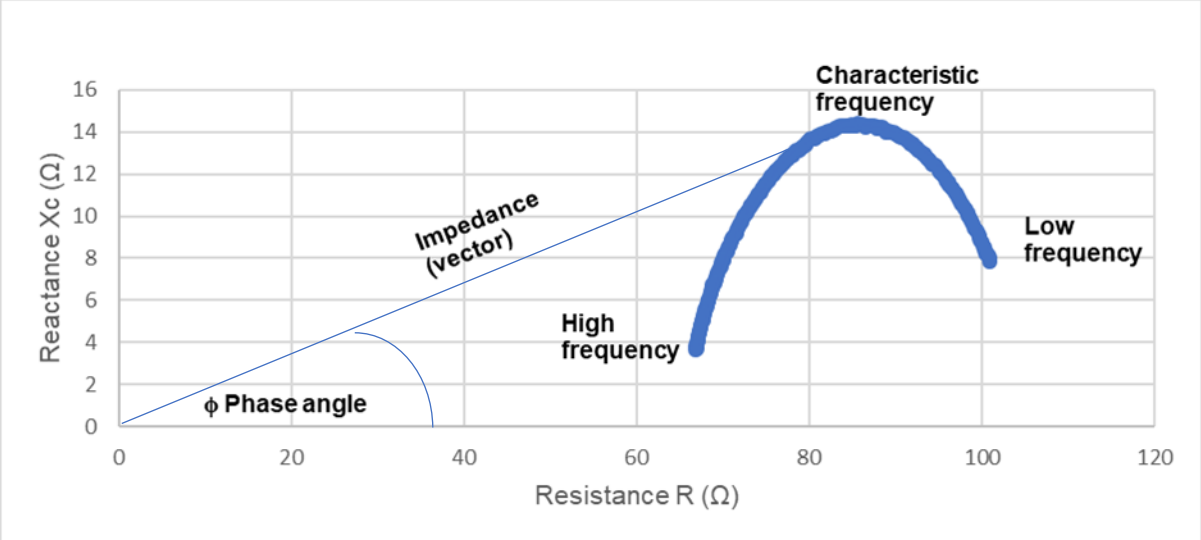
$$|Z| = \sqrt{R^2 + Xc^2} \quad \textbf{Equation 4}$$

$$\Phi = \tan^{-1}\left(\frac{Xc}{R}\right) \quad \textbf{Equation 5}$$

Where Φ is the phase angle between the reactance (Xc) and the resistance (R).

The variation of reactance and resistance with frequency is referred to as a Cole-Cole plot and an example is shown in **Figure 2.4.** This shows graphically that the maximum reactance, the peak of the plot, allows calculation of the characteristic frequency. The impedance and the phase angle at the characteristic frequency can then be calculated.

Figure 2.4 Example Cole-Cole Plot showing how the impedance and phase angle at the characteristic frequency (the peak) is calculated.



2.5 Relating theory to measurements

As described above, for each participant the following parameters were measured directly: age; height, weight; waist size.

The ImpediMed IMP^{TM} SFB7 bioimpedance meter measured: impedance, resistance, reactance and phase angle over the range of 5Hz to 500kHz frequency.

It then collated the raw data for download and also calculated the values shown in **Table 2.1.**

Table 2.1 ImpediMed IMP^{TM} SFB7 calculated values

Cole centre Characteristic resistance Rc	Resistance value of the centre of the Cole semicircle fitted to the data
Cole centre Characteristic reactance Xc	Reactance value at the centre of the Cole semicircle fitted to the data
Cole circle Radius	Radius of the Cole semicircle
Resistance at zero frequency (direct current) R_0	Predicted body resistance at zero frequency
Resistance at infinite frequency (pure alternating current) R_{inf}	Predicted body resistance at infinite frequency
Resistance of extracellular tissue Re	As for R_0
Resistance of intracellular tissue Ri	As for R_{inf}
Impedance at the characteristic frequency, Zc (ohms)	Predicted magnitude of body impedance at the Characteristic Frequency (as defined below)
Characteristic frequency Fc (Hz)	Frequency when reactance is maximum
Membrane capacitance c (farads)	Value of capacitance in the Cole equivalence circuit

The IMP^{TM} SFB7 applies a constant current, and the data above were calculated for each of the 10 scans through the frequency range 5kHz to 500kHz. The values for each experimental condition were then averaged. For example, data for Participant 5 with passive muscles on the first measurement scan are shown in **Table 2.2** below.

From this data the phase angle was calculated from each file using **Equation 5** with Xc calculated from the Zc, the impedance at the Characteristic Frequency and Cole fit centre R value, using **Equation 4**, see **Table 2.3** below. The mean and standard deviation (SD) were also then calculated for each set of readings.

Table 2.2 IMP^{TM} SFB7 Calculated values as per Table 2.1 during the first passive scan for participant 5.

	IMP^{TM} SFB7 file name										Mean	SD
	284	285	286	287	288	289	290	291	292	293		
Cole fit centre X, ohms	-7.61	-7.72	-7.71	-7.59	-7.68	-7.70	-7.77	-7.75	-7.73	-7.73	-7.70	0.05
Cole fit centre R, ohms	85.42	85.39	85.47	85.47	85.46	85.44	85.40	85.37	85.43	85.41	85.43	0.03
Cole circle radius, ohms	21.95	22.05	22.00	21.94	22.02	22.03	22.10	22.07	22.05	22.08	22.03	0.05
R (zero), ohms	106.00	106.05	106.08	106.06	106.09	106.08	106.09	106.03	106.09	106.09	106.07	0.03
R (infinity), ohms	64.84	64.74	64.87	64.89	64.83	64.79	64.71	64.71	64.78	64.73	64.79	0.06
Re, ohms	106.00	106.05	106.08	106.06	106.09	106.08	106.09	106.03	106.09	106.09	106.07	0.03
Ri, ohms	166.96	166.18	167.00	167.13	166.66	166.46	165.93	166.03	166.33	166.05	166.47	0.42
Z characteristic, ohms	86.62	86.59	86.66	86.67	86.65	86.63	86.59	86.56	86.63	86.60	86.62	0.03
f characteristic, kHz	29.98	29.97	30.04	29.94	29.96	29.94	29.94	29.99	30.00	29.99	29.97	0.03
Membrane capacitance, nF	19.45	19.51	19.40	19.46	19.48	19.51	19.54	19.50	19.47	19.50	19.48	0.04

The numbers along the top indicate the IMP^{TM} SFB7 file name.

Table 2.3 Calculated phase angle for the first passive muscle scan for participant 5

	IMP^{TM} SFB7 file name										Mean	SD
	284	285	286	287	288	289	290	291	292	293		
Phase angle (degrees)	9.52	9.53	9.49	9.53	9.52	9.53	9.52	9.52	9.52	9.53	9.52	0.01

Phase angle has been shown to be a sensitive indicator of muscle decline (Uemura et al., 2020) and has also been used in studies of nutritional status, disease progression and mortality risk.

2.6 Data analysis

Data were tested for normality in order to choose the most appropriate test for statistical significance, however, parametric tests which assume normality are relatively tolerant to violations (Pallant, 2016, p. 227). Normality was tested using quantile-quantile (Q-Q) plots and the Shapiro-Wilk test.

Unfortunately, the sample size is small and this will affect the power of the statistical tests.

If data are normally distributed then data analysis will be carried out using a paired t-test for the data relating to intra-subject measurements. To test the first two hypotheses a significance level of 0.05 was chosen. The electrical impedance myography (EIM) results may be considered significant if the measurement is the same or very similar 95% of the time and there is a 5% chance that it is random.

If data are normal a Pearson correlation analysis will be carried out for measurements, to test a possible relationship with age and demographic-derived data. To test the second two hypotheses electrical impedance myography (EIM) variation with age will be tested with individual age data as well as using age groups 18-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90, 91-100 and a significance level of 0.05 was chosen. An additional analysis of age-related data will be carried out using two age groups: under 40 years old and over 40 years old. This age delineation is derived from Keller and Engelhardt (2013). t-test statistics will be used to test

whether the mean EIM measurements are the same in these two age groups. Mann-Whitney U Test (‘Mann-Whitney U Test’, 2022) analysis may also be used to test for statistical significance between the two groups if the data sample is not shown to be normal.

Data will also be tested for a cycle effect between the two cycles described. Variance of impedance and phase angle with age will also be tested using one-way ANOVA.

3 Results of the clinical trial using electrical impedance myography (EIM)

The research question investigated was: Can electrical impedance measurements of muscles be used to assess muscle health?

To restate the hypotheses:

- The impedance of passive and active muscle is the same.
- The impedance phase angle of passive and active muscle is the same.
- The impedance of muscle varies with age.
- The impedance phase angle of muscle varies with age.

The null hypotheses are:

- Impedance of passive and active muscle is the same.
- Phase angle of passive and active muscle is the same.
- Impedance of muscles in adults is independent of age.
- Impedance phase angle of muscle is independent of age.

A significance level of 0.05 was chosen

The second hypothesis was also explored using age groups. Chosen age groups were 18-30, 31-40, 41-50, 51-60, 61-70 and 71 and over. It was also explored using data from participants aged <40 and >40 years of age.

3.1 Demographic data

Due to time constraints and practicality the study aimed to recruit 20 healthy volunteers, but it proved possible to recruit 25 who all met the inclusion criteria. 13 female and 12 male, age range 18 to 82 were included in this study to test the hypotheses. Measurements were made over a period of 6 months. Demographic

data is shown in **Table 3.1 to Table 3.5.** These indicate a balanced number of male and female participants, a wide age range and a balanced range of participants over and under 40 years of age, indicating that although the study is small it has achieved some balance in these areas. These are further discussed in **Section 4: Discussion**.

Table 3.1 Demographic data, n = 25

	Mean	Median	SD	Range	Minimum	Maximum
Age (years)	43	38	16.76	64	18	82
Height (cm)	171.4	172.0	11.4	44.5	151.0	195.5
Weight (kg)	78.8	75.2	19.31	87.0	51.8	138.8
Waist circumference (cm)	90.9	89.0	12.89	46.0	69.0	115.0

Table 3.2 Data for male participants, n = 12

	Mean	Median	SD	Range	Minimum	Maximum
Age (years)	36	31	13.99	44	18	62
Height (cm)	178.3	176	7.13	27.0	168.5	195.5
Weight (kg)	87.2	86.0	19.1	77.6	61.2	138.8
Waist circumference (cm)	96.0	97.0	10.37	33.0	82.0	115.0

Table 3.3 Data for female participants, n = 13

	Mean	Median	SD	Range	Minimum	Maximum
Age (years)	50	54	16.42	58	24	82
Height (cm)	163.9	163	10.39	41.0	151.0	192.0
Weight (kg)	69.7	65.6	14.94	54.5	51.8	106.3
Waist circumference (cm)	85.3	82.0	13.01	41.0	69.0	110.0

Table 3.4 Participants sorted into five age groups, n = 25

Age group (years)	Participants	Male	Female
18 to 30	8	6	2
31 to 40	5	3	2
41 to 50	2	1	1
51 to 60	5	2	3
61 to 70	4	1	3
71 to 82	1	0	1

Table 3.5 Participants sorted into two age groups, n = 25

Age group (years)	Participants	Male	Female
18 to 40	13	9	4
41 and over	12	4	8

3.2 Check for normality

Since the sample size was small (n=25), determining the distribution of the participants' age and impedance data was important for choosing an appropriate statistical test. The data were tested for normality with quantile-quantile (Q-Q) plots and the Shapiro-Wilk test.

Figure 3.1 Quantile-Quantile (Q-Q) plot for muscle impedance from 25 participants to test for normal distribution of data

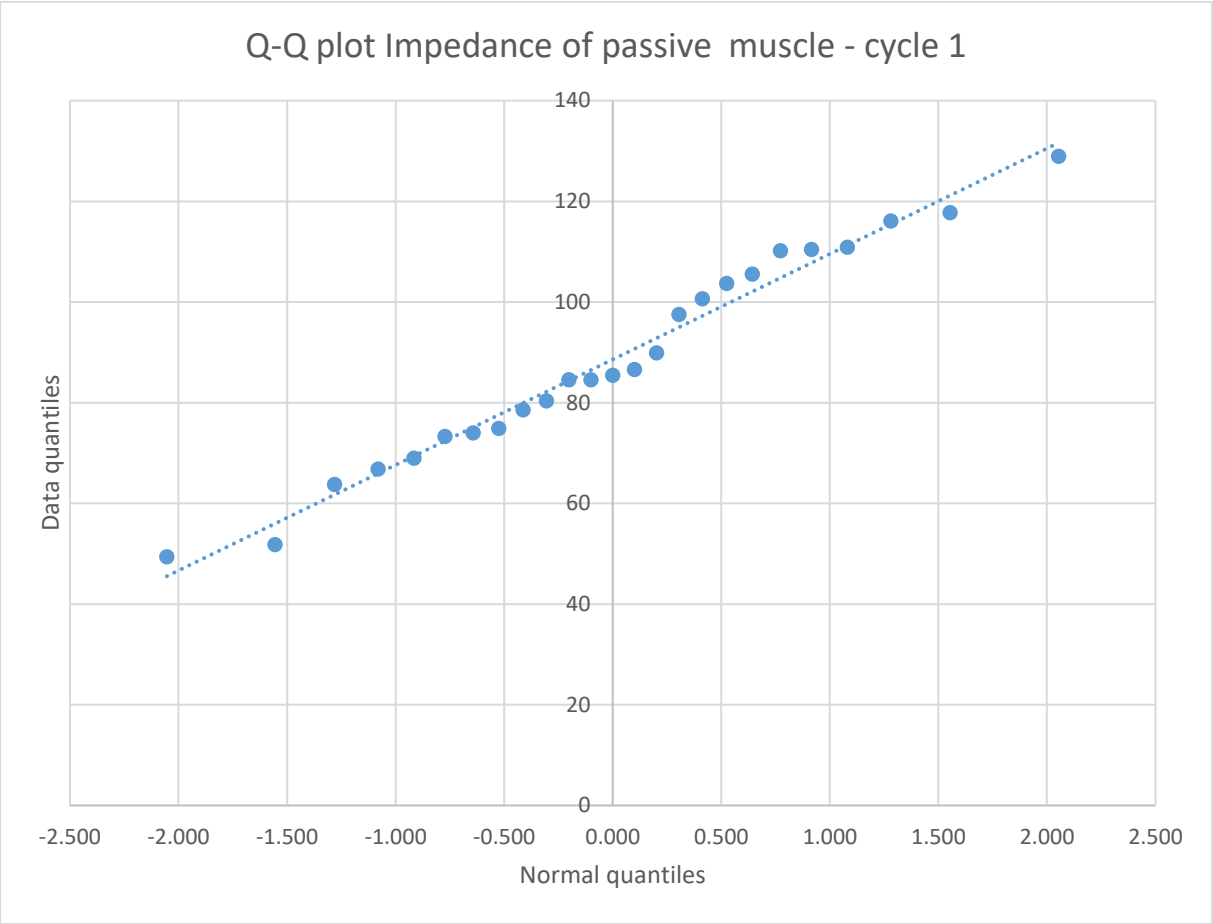
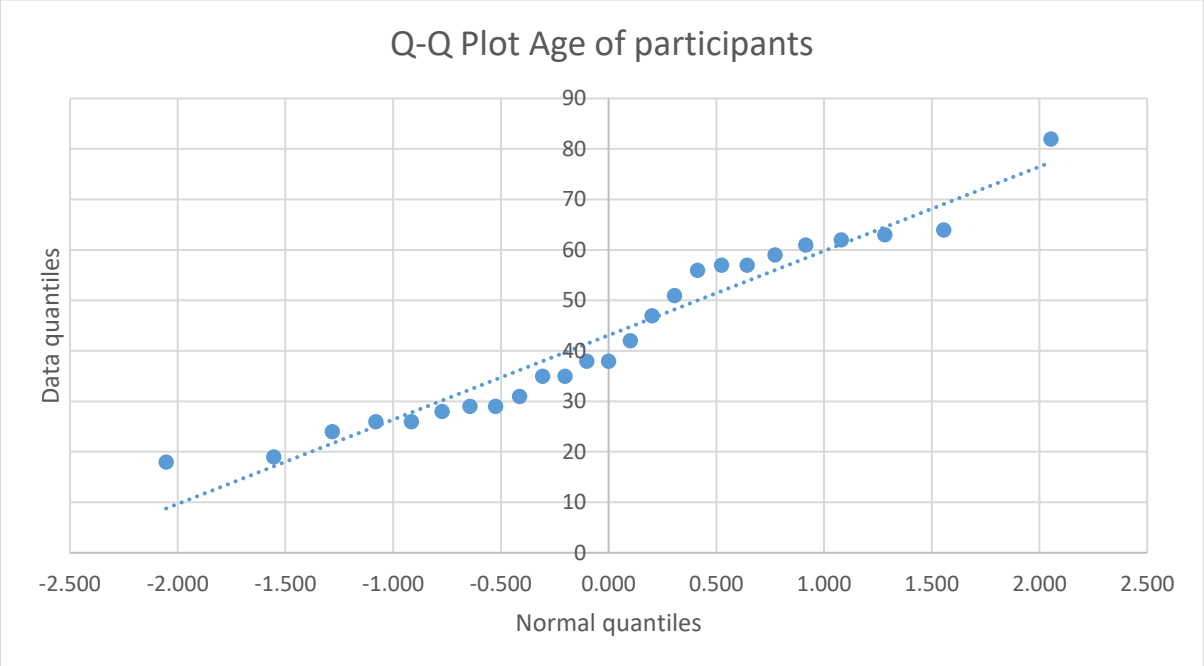


Figure 3.2 Quantile-Quantile (Q-Q) plot of age distribution for 25 participants to test for normal distribution of data



The size of the sample inhibits some of the representation of normality, but the quantile-quantile (Q-Q) plots, as shown in **Figures 3.1 and 3.2** above, provide moderate evidence that it is appropriate to use normal distribution statistics. The Shapiro-Wilk test is considered a more powerful test of data normality (Razali and Wah, 2010). The Shapiro-Wilk test was performed and showed that the distribution of impedance of passive muscle was close to normality ($W(25) = 0.97$, since p-value = 0.75 is greater than the α value of 0.05). The Shapiro-Wilk test was also performed for the age of participants' distribution and showed that the data was close to normality ($W(25) = 0.94$, and the p-value = 0.19 is greater than the α value of 0.05). This indicates the likelihood of normality which may be used to indicate which statistical test may be used for analysis.

3.3 Cole-Cole plot

Electrical impedance myography (EIM) measurements of passive and active muscles were taken using the agreed protocol as described in **Section 2**. The participants were rested before the first passive measurement and then again after the first active measurement, following the protocol:

Rest

Measurement of passive muscle

Measurement of active muscle

Rest for 5 minutes

Measurement of passive muscle

Measurement of active muscle.

Reactance Xc (Ω) is plotted against Resistance R (Ω) for the range of frequencies in a Cole-Cole plot as described in **Appendix 3,** see also the example in **Figure 2.4**. Zc, impedance at the Characteristic Frequency is calculated from the peak value of Xc and R using **Equation 4.**

The mean Zc value was calculated for the 10 scans for each condition (passive, active, passive, active) as described.

3.4 Characteristic results data

Data for the participants are shown in **Table 3.6.** The mean and standard deviation (SD) are calculated for each set of data. The body mass index (BMI) and the relative fat mass (RFM) have been calculated using **Equations 6, 7a and 7b**. The impedance at the Characteristic Frequency has been calculated as described and the mean and SD tabulated.

$$\mathrm{BMI} = \frac{\text{weight (kg)}}{(\text{height (m)})2}$$ **Equation 6**

For males

$$\mathrm{RFM} = 64 - 20\left(\frac{\text{height (cm)}}{\text{waist circumference (cm)}}\right)$$ **Equation 7a**

For females

$$\mathrm{RFM} = 76 - 20\left(\frac{\text{height (cm)}}{\text{waist circumference (cm)}}\right)$$ **Equation 7b**

Table 3.6 Characteristic data: mean and standard deviation (SD)

Characteristic data	Mean ± SD
Number	25
Age (years)	43 ±16.76
Height (cm)	171.40 ± 11.40
Weight (kg)	78.76 ±19.31
Body mass index (BMI) (kg/m$^{2)}$	26.70 ± 5.42
Relative fat mass (RFM) (%)	26.121 ± 5.62
Zc (passive cycle 1) (Ω)	88.59 ± 20.62
Zc (active cycle 1) (Ω)	84.70 ± 19.95
Zc (passive cycle 2) (Ω)	90.56 ± 21.37
Zc (active cycle 2) (Ω)	86.79 ± 20.12
PA (passive cycle 1) (degrees)	8.14 ± 1.97
PA (active cycle 1) (degrees)	8.41 ± 2.12
PA (passive cycle 2) (degrees)	8.18 ± 1.96
PA (active cycle 2) (degrees)	8.46 ± 2.15

As for **Table 3.6**, **Table 3.7** shows the data for the participants but split by gender

Table 3.7 Characteristic data: mean and standard deviation (SD) by gender

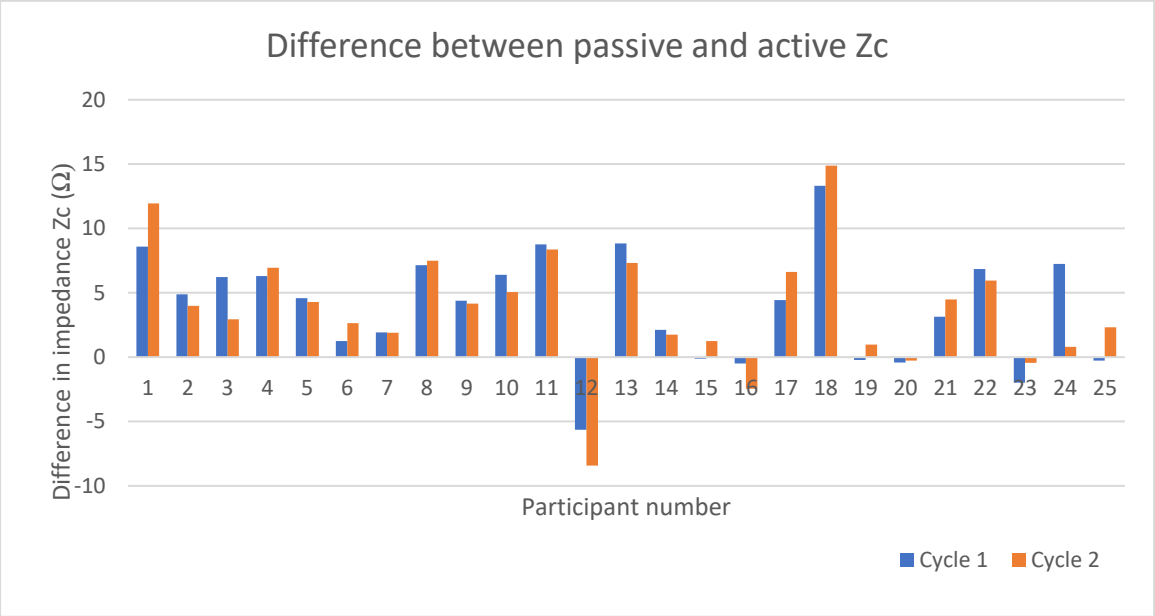
Characteristic data	Female (Mean ± SD)	Male (Mean ± SD)
Number	12	13
Age (years)	50.42 ± 16.42	36.31 ± 13.99
Height (cm)	163.92 ± 10.39	178.31 ± 7.13
Weight (kg)	69.68 ± 14.94	87.15 ±19.10
Body mass index (BMI) (kg/m$^{2)}$	26.05 ±5.92	37.30 ± 4.84
Relative fat mass (RFM) (%)	25.71 ± 7.11	26.50 ±3.70
Zc (passive cycle 1) (Ω)	106.35 ± 11.72	72.19 ± 11.45
Zc (active cycle 1) (Ω)	102.21 ±12.23	68.53 ± 9.10
Zc (passive cycle 2) (Ω)	108.68 ± 12.16	73.84 ±12.62
Zc (active cycle 2) (Ω)	104.14 ±12.23	70.77 ± 10.29
PA (passive cycle 1) degrees)	6.69 ± 1.23	9.47 ± 1.53
PA (active cycle 1) (degrees)	6.91 ± 1.33	9.79 ± 1.74
PA (passive cycle 2) (degrees)	6.75 ± 1.27	9.50 ± 1.49
PA (active cycle 2) (degrees)	6.92 ± 1.35	9.88 ± 1.74

The split by gender is important in order to assess if gender differences can be seen. Further analysis of the data and the variation of electrical impedance myography (EIM) parameters, Zc and phase angle with age, gender and body fat percentage, as calculated from body mass index (BMI) are also tested.

3.5 Impedance at the Characteristic Frequency, Zc

The difference between the mean Zc for each of the two passive-active cycles is shown for each participant in **Figure 3.3**. This figure suggests that there is a difference in impedance between passive and active muscle. It has already been shown that the data are (statistically likely to be) normally distributed using the Shapiro-Wilk test. Therefore, parametric statistical tests are applied.

Figure 3.3 Represents the difference in Zc (Impedance at the Characteristic Frequency), for each participant in each measurement cycle



A paired t-test with $\alpha \leq 0.05$ using the Zc data in passive and active muscles for each participant for each of the two cycles was carried out using Microsoft Excel (2019). The results are shown in **Table 3.8.**

Cycle 1: t = 4.56, calculated $p \leq 0.01$ indicating rejection of the null hypothesis, i.e. impedance in passive and active muscles is not the same.

Cycle 2: t = 4.06, calculated $p \leq 0.01$ indicating rejection of the null hypothesis.

Table 3.8 Paired t-tests for impedance at the Characteristic Frequency data

Cycle 1 t-Test: Paired Two Sample for Means		
	Variable 1	*Variable 2*
Mean	88.59	84.70
Variance	443.05	414.47
Observations	25.00	25.00
Pearson Correlation	0.98	
Hypothesized Mean Difference	0.00	
df	24.00	
t Stat	4.56	
P(T<=t) one-tail	0.00	
t Critical one-tail	1.71	
P(T<=t) two-tail	0.00	
t Critical two-tail	2.06	
Cycle 2 t-Test: Paired Two Sample for Means		
	Variable 1	*Variable 2*
Mean	90.56	86.79
Variance	475.78	421.74
Observations	25.00	25.00
Pearson Correlation	0.98	
Hypothesized Mean Difference	0.00	
df	24.00	
t Stat	4.06	
P(T<=t) one-tail	0.00	
t Critical one-tail	1.71	
P(T<=t) two-tail	0.00	
t Critical two-tail	2.06	

Sample size is a concern but this was a feasibility study limited by funding and time. A post-hoc power calculation using the above data results in power of 0.1 which

indicates that if the null hypothesis is false, there is a 90% chance that it could not be rejected with such a small sample size.

3.5.1 Ratios

The ratio of the mean Zc for passive and active muscle can be calculated and shows an interesting trend. From **Table 3.6:**

Cycle 1: Passive Zc/Active Zc = 88.59/84.70 = 1.045

Cycle 2: Passive Zc/Active Zc = 90.56/86.79 = 1.043

And for the split by gender from **Table 3.7:**

Female

Cycle 1: Passive Zc/Active Zc = 1.041

Cycle 2: Passive Zc/Active Zc = 1.044

Male

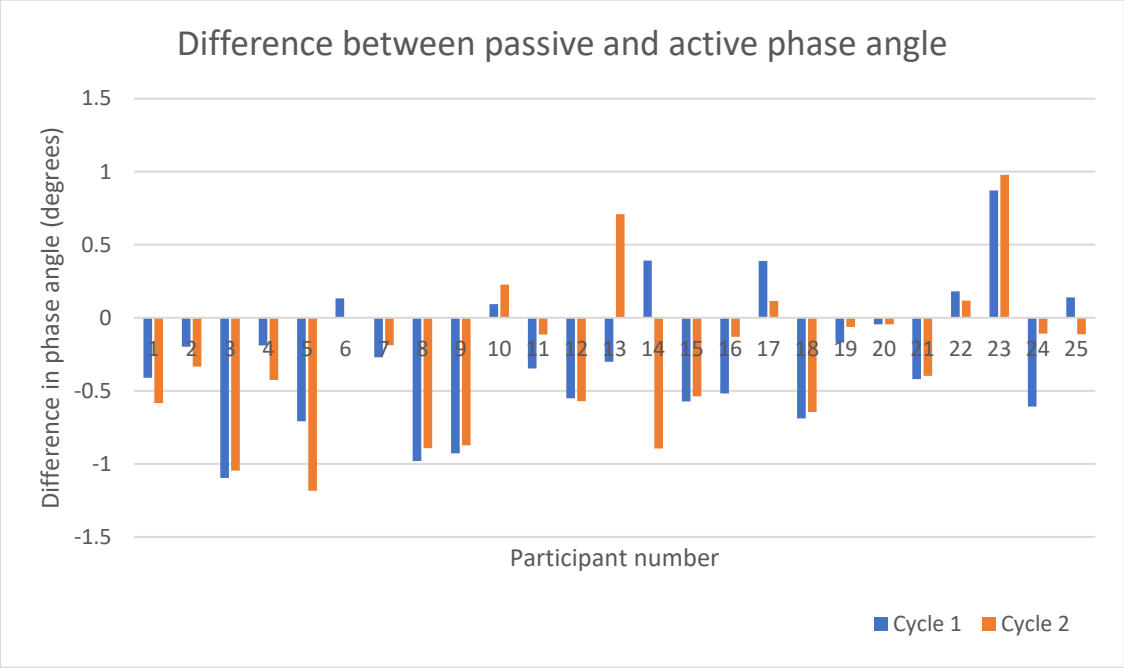
Cycle 1: Passive Zc/Active Zc = 1.053

Cycle 2: Passive Zc/Active Zc = 1.043

3.6 Phase angle at the Characteristic Frequency

The difference between the mean phase angle for each of the two passive-active cycles is shown for each participant in **Figure 3.4**. This figure suggests that there is a difference in phase angle between passive and active muscle.

Figure 3.4 Represents the difference in phase angle (at the Characteristic Frequency), for each participant in each measurement cycle



A paired t-test with $\alpha \leq 0.05$ using the phase angle (PA) data in passive and active muscles for each participant for each of the two cycles was carried out using Microsoft Excel (2019). The results are shown in **Table 3.9**.

Cycle 1: t = -2.90, calculated $p \leq 0.01$ indicating rejection of the null hypothesis, i.e. PA in passive and active muscles at the Characteristic Frequency is not the same.

Cycle 2: t = -2.72, calculated $p \leq 0.01$ indicating rejection of the null hypothesis.

Table 3.9 Paired t-tests for phase angle at the Characteristic Frequency data

Cycle 1 Paired t tests for phase angle t-Test: Paired Two Sample for Means		
	Variable 1	*Variable 2*
Mean	8.14	8.41
Variance	3.87	4.49
Observations	25.00	25.00
Pearson Correlation	0.98	
Hypothesized Mean Difference	0.00	
df	24.00	
t Stat	-2.90	
P(T<=t) one-tail	0.00	
t Critical one-tail	1.71	
P(T<=t) two-tail	0.01	
t Critical two-tail	2.06	
Cycle 2 t-Test: Paired Two Sample for Means		
	Variable 1	*Variable 2*
Mean	8.18	8.46
Variance	3.82	4.63
Observations	25.00	25.00
Pearson Correlation	0.97	
Hypothesized Mean Difference	0.00	
df	24.00	
t Stat	-2.72	
P(T<=t) one-tail	0.01	
t Critical one-tail	1.71	
P(T<=t) two-tail	0.01	
t Critical two-tail	2.06	

3.6.1 Ratios

The ratio of the mean phase angle for passive and active muscle can be calculated and shows an interesting trend. From **Table 3.6**

Cycle 1: Passive PA/Active PA = 8.14/8.41 = 0.968

Cycle 2: Passive PA/Active PA = 8.18/8.46 = 0.967

And for the split by gender from **Table 3.7**

Female

Cycle 1: Passive PA/Active PA = 0.968

Cycle 2: Passive PA/Active PA = 0.975

Male

Cycle 1: Passive PA/Active PA = 0.967

Cycle 2: Passive PA/Active PA = 0.962

3.7 Variation of Zc with age

Participants' ages ranged from 18 to 82 years (mean = 43 years, SD = 16.76 years), 52% identified as male, 48% identified as female.

Figure 3.5 below shows impedance, Zc, of passive muscle against the age of the participants. Pearson correlation coefficient r (23) = .6, p = .002 indicating a strong (Evans, 1996) positive correlation between age and Zc.

Figure 3.5 Impedance against age: passive cycle 1. Demonstrating a positive correlation between age and impedance.

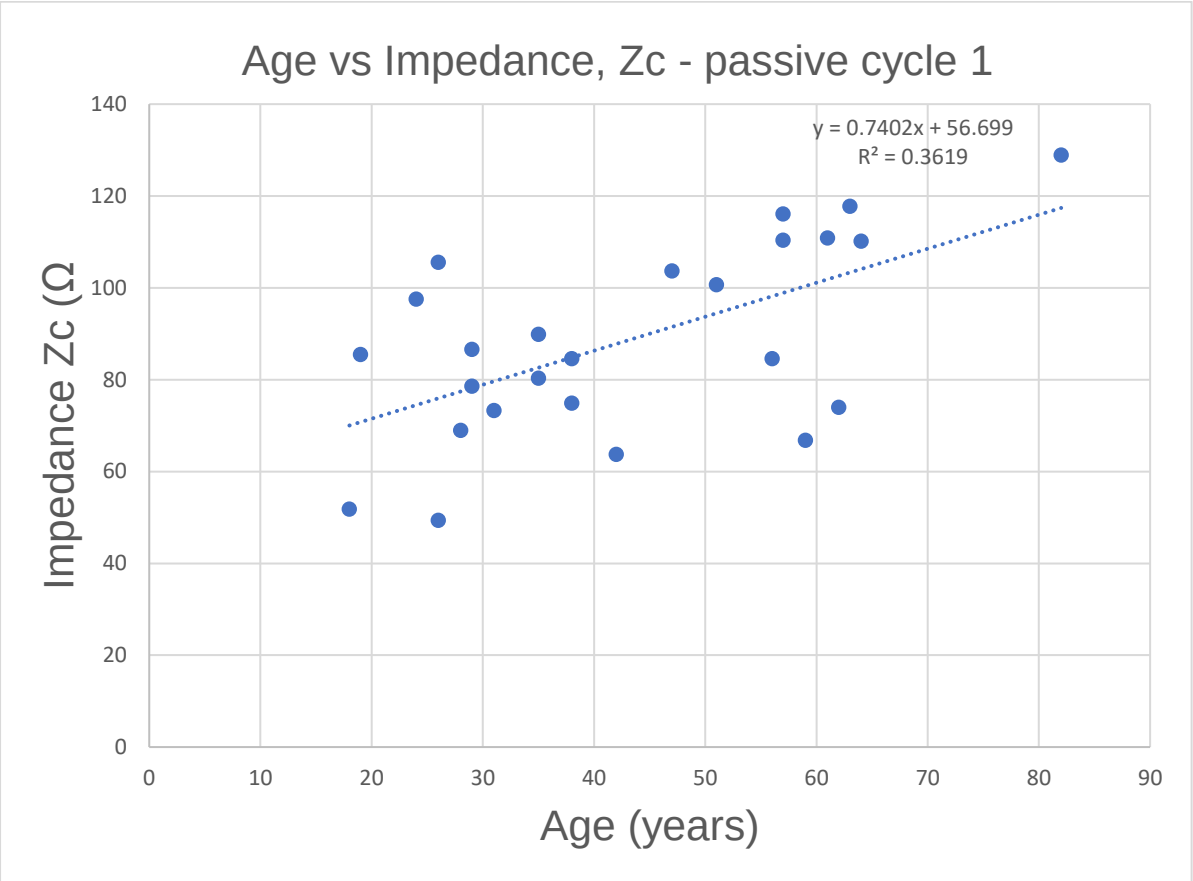


Table 3.10 shows the Pearson correlation for the four scans of impedance measurements with age.

Table 3.10 Pearson correlation age versus impedance data

Scan	Pearson correlation coefficient	Degrees of freedom	*p* value
Passive 1	0.60	23	0.001
Active 1	0.57	23	0.003
Passive 2	0.60	23	0.002
Active 2	0.55	23	0.004

This demonstrates that for passive and active muscle there is a significant positive correlation between the impedance at the Characteristic Frequency and age.

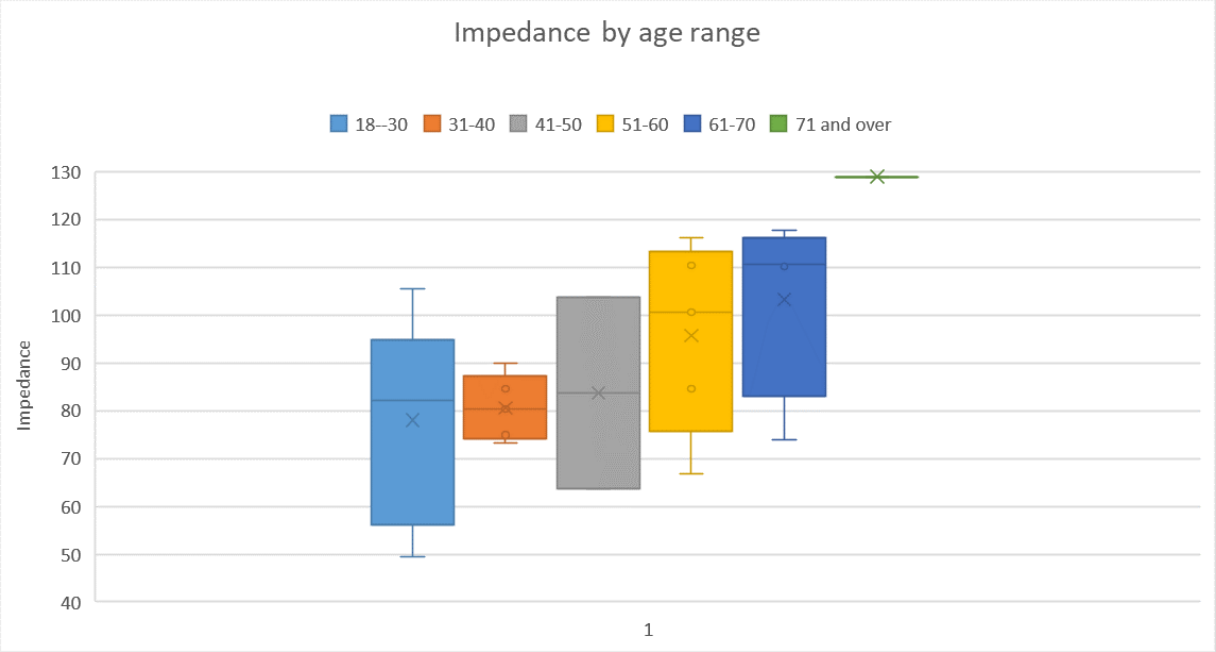
However, in **Figure 3.5** it can be seen that for the passive cycle 1 the coefficient of determination indicates a weak linear regression model relationship, $R^2 = 0.36$ as shown by the trendline and the equation on the figure. The linear regression equations and R^2 are calculated for each of the four cycles and are shown in **Table 3.11.**

Table 3.11 Linear regression and R^2 for age against impedance at the Characteristic Frequency for the four scans

Scan	Linear regression equation	R^2
Passive 1	y = 0.74x + 56.70	0.36
Active 1	y = 0.69x + 55.23	0.33
Passive 2	y = 0.76x + 57.62	0.36
Active 2	y = 0.67x + 58.10	0.31

The use of age groups to test the hypothesis is shown below. Age groups: 18-30, 31-40, 41-50, 51-60, 61-70 and 71 and over, were used and are plotted as a box and whisker plot in **Figure 3.6**. A stronger linear regression correlation is seen, $R^2 = 0.87$.

Figure 3.6 Impedance at the Characteristic Frequency, Zc, against age group: passive scan 1 – a box and whisker plot



However, there are only 25 participants and as can be seen in **Table 3.4** participants in the age groups are not equally distributed and in the highest age group there is only one participant.

To check the validity of the correlation calculations a one-way ANOVA was calculated for the six-age group analysis. This shows that the mean Zc for passive muscle for these age groups is not significantly different (at the 0.05 level), $p = 0.09$, $F = 2.29$, $df = 24$; since the p value is > 0.05. However, as the p value was close to the 0.05 significance level this could be indicative of low study power due to the small sample size.

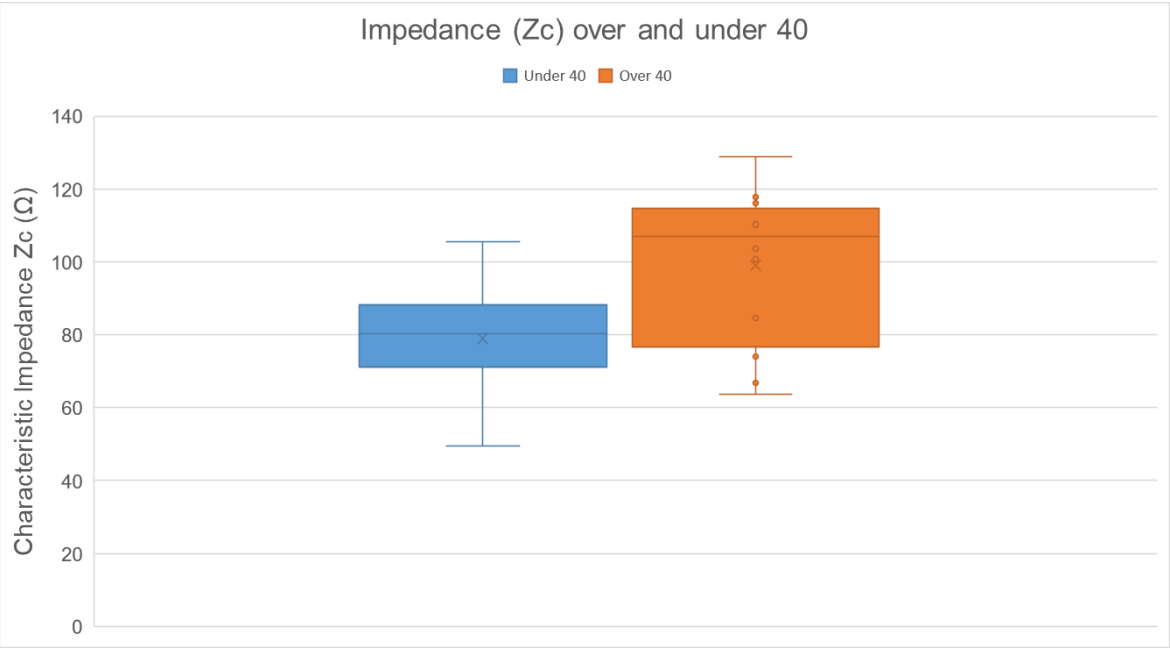
As described in the methodology an additional method is used to analyse the data since there are only 25 participants and these are not equally spaced across the six age groups. Participants are divided into two groups: under and over 40 years old. No participant was exactly 40 years old. The characteristic data is shown in **Table**

3.12. The impedance during the first passive scan is shown in a box and whisker plot in **Figure 3.7.**

Table 3.12 Characteristic data: for two age groups

Characteristic data	Age < 40 years	Age > 40 years
Number	13	12
Age (years)	28.92 ± 6.47	58.42 ± 9.97
Height (cm)	162.86 ± 10.48	167.08 ± 47.67
Weight (kg)	77.83 ± 22.37	79.78 ± 27.64
Body mass index (BMI) ($kg/m^{2)}$	24.92 ± 4.52	28.63 ± 9.96
Relative fat mass (RFM) (%)	23.50 ± 3.85	28.96 ± 10.00
Zc (passive cycle 1) (Ω)	78.99 ± 15.99	98.98 ± 34.30
Zc (active cycle 1) (Ω)	75.59 ± 14.03	94.55 ± 33.66
Zc (passive cycle 2) (Ω)	80.58 ± 17.17	101.38 ± 34.96
Zc (active cycle 2) (Ω)	77.70 ± 14.79	96.63 ± 34.01
PA (passive cycle 1) degrees)	9.28 ± 1.71	6.95 ± 1.44
PA (active cycle 1) (degrees)	9.71 ± 1.80	7.00 ± 1.44
PA (passive cycle 2) (degrees)	9.33 ± 1.66	6.93 ± 1.44
PA (active cycle 2) (degrees)	9.79 ± 1.84	7.01 ± 1.42

Figure 3.7 Impedance at the Characteristic Frequency, Zc, over and under 40 years of age: passive scan 1 – a box and whisker plot



A two-sample t-test was performed to compare Zc passive muscle of participants under 40 years of age with Zc passive muscle of participants over 40 years of age. This analysis was repeated with the phase angle.

There was a significant difference in Zc between under 40 (M = 78.99, SD = 15.99) and over 40 (M = 98.98, SD = 34.30); t (23) = 2.07, *p* = 0.014.

There was a significant difference also seen in phase angle (PA) between under 40 (M = 9.28, SD = 1.71) and over 40 (M = 6.95, SD = 1.44); t (23) = 2.07, *p* = 0.001.

As the sample size is small, the results were also tested using the Mann-Whitney U test although the Shapiro-Wilk test had demonstrated a normal distribution. The Mann-Whitney U test showed that:

> the Zc of passive muscle in the participants under 40 years old and over 40 years old was significantly different (U = 38 p = 0.013) for a chosen significance level of 0.05.
>
> the impedance phase angle in participants under 40 years old and over 40 years old was significantly different (U = 25 p = 0.002) for a chosen significance level of 0.05.

3.7.1 Ratios

The ratio of the mean Zc for passive and active muscle for the two age groups can be calculated and shows an interesting trend. From **Table 3.12:**

Under 40

Cycle 1: Passive Zc/Active Zc = 1.045

Cycle 2: Passive Zc/Active Zc = 1.037

Over 40

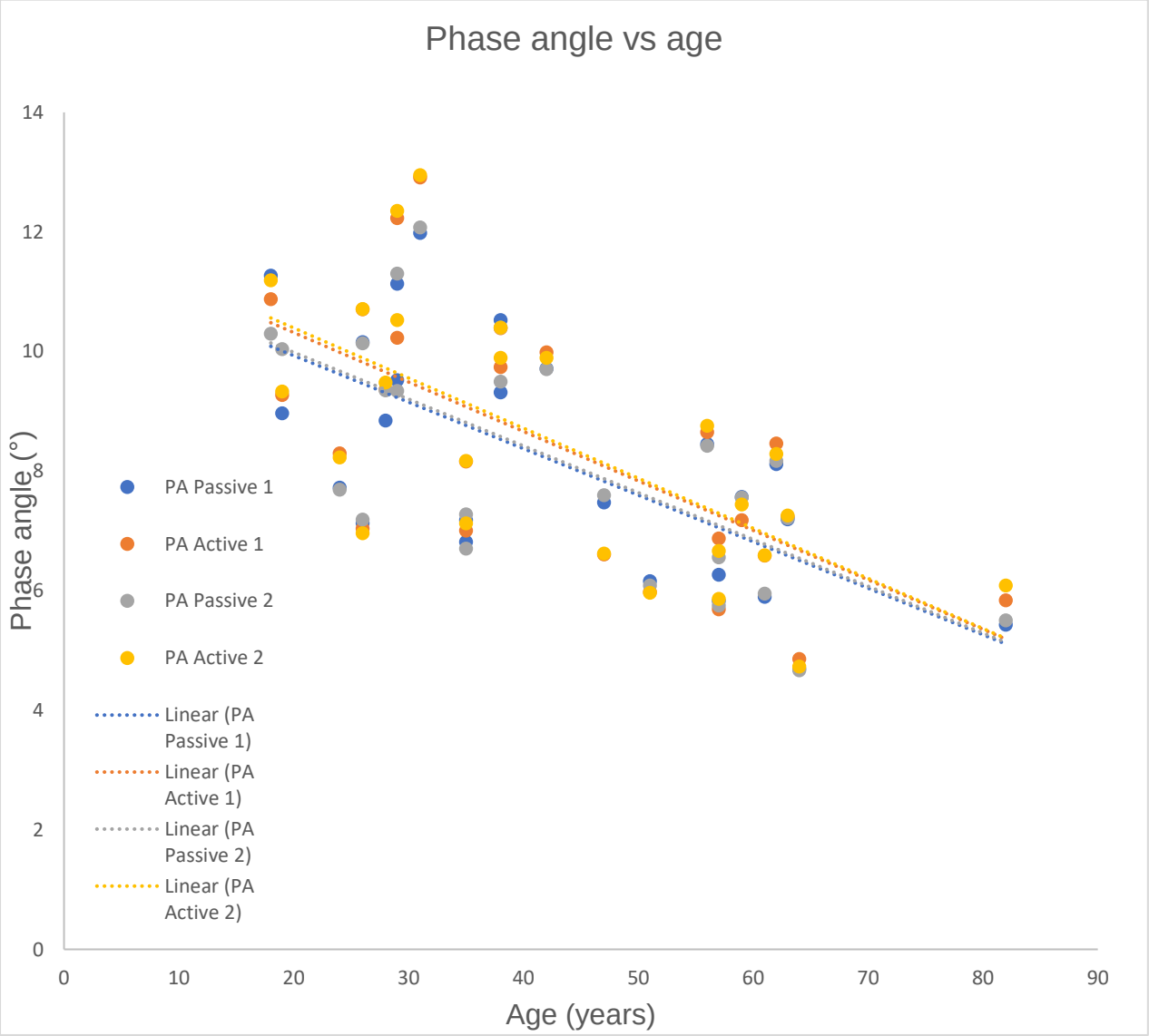
Cycle 1: Passive Zc/Active Zc = 1.047

Cycle 2: Passive Zc/Active Zc = 1.049

3.8 Variation of phase angle with age

The variation of phase angle with age in healthy adults is shown in **Figure 3.8** below.

Figure 3.8 Phase angle against age for both cycles. Demonstrating a negative correlation



Where PA = phase angle

Pearson correlation was applied to the phase angle data and is shown in **Table 3.13**.

A statistically significant strong negative correlation is seen for all four scans r (23) = -0.68 $p < 0.001$

Table 3.13 Pearson correlation: age and phase angle for all four scans

Scan	Pearson correlation coefficient	Degrees of freedom	*p* value
Passive 1	-0.68	23	<0.001
Active 1	-0.67	23	<0.001
Passive 2	-0.68	23	<0.001
Active 2	-0.67	23	<0.001

P values 0.0002

The linear regression was also calculated and found to be weaker, but stronger than the regression with impedance at the Characteristic Frequency; R^2, did not exceed 0.5. This is shown in **Table 3.14**.

Table 3.14 Linear regression and R^2 for age and phase angle at the Characteristic Frequency for the four scans

Scan	Linear regression equation	R^2
Passive 1	y = -0.078x + 11.49	0.458
Active 1	y = -0.083x + 11.97	0.446
Passive 2	y = -0.079x + 11.55	0.469
Active 2	y = -0.084x + 12.07	0.444

3.8.1 Ratios

The ratio of the mean phase angle for passive and active muscle in the two age groups can be calculated and shows an interesting trend. From **Table 3.12:**

Under 40 years old

Cycle 1: Passive PA/Active PA = 0.956

Cycle 2: Passive PA/Active PA = 0.953

Over 40 years old

Cycle 1: Passive PA/Active PA = 0.993

Cycle 2: Passive PA/Active PA = 0.989

3.9 Variation by gender

The statistical significance of the differences seen between the genders in **Table 3.15** was tested. Participants identifying as female = 12, identifying as male = 13. Degrees of freedom = 23, α = 0.05 chosen, t critical two-tail = 2.07 two sample t-test assuming equal variance. Assuming a null hypothesis of no difference between male and female Zc or phase angle.

Table 3.15 Gender: Zc and phase angle t-test two-sample assuming equal variance

Parameter	T stat	P(T≤t) two-tail	Accept/reject null hypothesis
Zc Passive 1	7.07	0.00	Reject
Zc Active 1	7.53	0.00	Reject
Zc Passive 2	6.73	0.00	Reject
Zc Active 2	7.10	0.00	Reject
Phase Angle Passive 1	-4.96	0.00	Reject
PA Active 1	-4.61	0.00	Reject
PA Passive 2	-4.94	0.00	Reject
PA Active 2	-4.72	0.00	Reject

3.10 Variation of impedance with body fat percentage

The variation of impedance, Zc, with calculated body fat percentage using the body mass index (BMI), were also examined. Body fat percentage was calculated using:

Body fat percentage = 1.2 x BMI +0.23 x age - 16.2	male	**Equation 8a**
Body fat percentage = 1.2 x BMI + 0.23 x age - 5.4	female	**Equation 8b**

Source: Bmisite.net (2022) and Gaiam.com (2022).
Other formulae are available but this is the most consistent. Body fat and body mass index (BMI) are highly correlated (Bradbury et al., 2016).

Table 3.16 Pearson correlation coefficient for body fat percentage

Scan	Pearson correlation coefficient	Degrees of freedom	*p* value
Passive 1	0.61	23	0.001
Active 1	0.64	23	<0.001
Passive 2	0.60	23	0.002
Active 2	0.60	23	<0.001

Table 3.16 shows that each scan demonstrates a significant Pearson correlation r (23) = 0.60 or greater p < 0.002. However, the regression linear equation is weak as seen in **Table 3.17**, with R^2 not exceeding 0.5 for any of the measurement scans.

Table 3.17 Linear regression and R2 for body fat percentage and impedance at the Characteristic Frequency for the four cycles

Scan	Linear regression equation	R^2
Passive 1	y = 1.18x + 51.97	0.377
Active 1	y = 1.20x + 47.54	0.415
Passive 2	y = 1.191x + 53.74	0.355
Active 2	y = 1.139x + 51.57	0.367

4 Discussion

From a review of the literature an objective and portable way to measure muscle health is still elusive. Ultrasound and manual methods can inform a health care professional on muscle health but a more objective and easier to use method would be of benefit. Electrical impedance myography (EIM) was identified as an emerging method of monitoring muscle health and it has been investigated here to test its applicability to muscle assessment in the clinic and in the community. To test whether measuring the impedance would be of benefit four hypotheses were stated. The basis for the hypotheses were that if the impedance or the impedance phase angle of passive and active muscle were the same this may indicate its use for patients who have limited voluntary muscle ability, i.e. are not able to move their muscles as they wish; secondly a test of impedance measurements across an age range may inform the change of muscle health with age and support sarcopenia and degenerating muscle disease research.

A clinical trial on healthy volunteers was approved. 25 healthy participants volunteered and were assessed and measured. This was a small-scale pilot feasibility study given the constraints of time and funding. It is recognised that higher power is required in order to be confident of the significance of the results.

The participant data were found to be normally distributed using a quantile-quantile (Q-Q) plot (**Figures 3.1** and **3.2**), although the sample was small.

4.1 Testing electrical impedance myography (EIM) measurement of active and passive muscle

The results demonstrated that the impedance at the Characteristic Frequency, Zc, of relaxed and active muscle as measured on the biceps brachii were significantly

different. A *p* value of 0.00013 was calculated indicating that the impedance, Zc, of passive and active muscle was different; the null hypothesis was therefore rejected. The statistics cannot describe how different the Zc values were, but **Figure 3.3** shows an inherent difference and **Table 3.6** a wide standard deviation in Zc.

It has been recognised that the Zc value, as described in **Table 2.1**, is 'a predicted magnitude of body impedance at the Characteristic Frequency' as calculated by the IMP^{TM} SFB7. As such, this value relates to assumptions made for the whole body rather than for the muscle being measured. This may have an impact on the results and tests against the hypotheses, in particular the first two hypotheses. Calculation of the impedance at the Characteristic Frequency for each scan through the frequencies relies on interpolation of maximum Xc based on a fitted polynomial equation. The calculated Zc from the interpolated Xc is found to be close to Zc as calculated by the IMP^{TM} SFB7. It can be considered a systematic error in that it is used in the data analysis.

The results also demonstrated that the impedance phase angle of passive and active muscle were significantly different.

Consideration of what may be the cause of the difference in Zc and phase angle between passive and active muscle is discussed below.

The health of the volunteers was screened to exclude those with active arthritis, heart disease and known neurological conditions which may have affected the electrical impedance myography (EIM) data. Skeletal muscle has a water content of approximately 70-75% (Lorenzo et al., 2019) divided between the extracellular water (ECW) and the intracellular water (ICW).

Other factors which may be considered are the skin condition of the volunteer, the estimated subcutaneous fat, blood flow, muscle fatigue, hydration, and general environment. The position of the electrodes may be a source of error or inconsistency (L. Li et al., 2016a).

The ratio of the mean Zc for passive and active muscle and also the ratio of the phase angle for passive and active muscle were calculated and show an interesting trend.

The active muscle is only partially activated but a consistent ratio between the passive and active Zc and phase angle values for both cycles may be significant. This can also be seen in the gender and age group values. More cycles and more participants would be needed to test this further. If a consistent ratio or relationship between the impedance and/or phase angle of active and passive muscle can be established, then the measurement of Zc on passive muscle may still be of value in assessing the muscle health. The ratio may possibly be a function of the percentage of activation of the muscle under observation but further measurement of different activation levels would be needed to explore this.

Care must be taken in considering the impedance values of these participants and not confusing the change with age and the change with active muscle.

As described by Sanchez and Rutkove (2017) and Cornish et al., (1993), the electrical properties of biological tissue are complex and difficult to unravel. Muscle is anisotropic and demonstrates different properties longitudinally and laterally. Muscle is a macroscopic tissue made up of muscle fibres encased in a sheath and the individual muscle fibres do not all activate contiguously since they are dependent on their motor neurones (see **Appendix 2**). In addition, there are nerve cells, blood

vessels and fascia. This Zc value calculated is the impedance at which the reactance due to the capacitance of the cell walls is a maximum and the ‘current is evenly divided between the intracellular and extracellular compartments’ (Sanchez and Rutkove, 2017; Foster and Schwan,1989). It can be seen that Zc is a more reliable value than the impedance at a specified frequency. This is particularly important when electrical impedance myography (EIM) is used to measure the health of the muscle because the capacitance of the cell walls gives a better indication than the resistance of the salt ions as described by many authors. Measuring the maximum reactance demonstrates the optimal capacitance.

4.2 Testing electrical impedance myography (EIM) measurements with age

A significant positive Pearson correlation of Zc with increasing age is seen in **Table 3.10** but the linear regression coefficient indicates a weak model relationship, with R^2 = 0.36. This may be as a result of the small sample and of other factors such as electrode position, subcutaneous fat and other factors discussed below. The Pearson correlation supports the research question which sought to link aging muscle changes to EIM measurement values. As discussed in **Section 1** changes in muscle with age have been documented by Goodpaster et al., (2006), Keller and Engelhardt (2013) and Vilaca et al., (2014) using other methods and different age cohorts.

Dividing the participant data into age groups and using a box and whisker plot demonstrates again the increase of Zc with age. However, the number of participants in the age groups are not equal. Again, a larger sample may better support the hypothesis.

Dividing the participants into two age groups, under and over 40 years of age demonstrated a significant difference in Zc and phase angle. The Mann-Whitney U test confirmed this. The analysis using two age groups, following Keller and Engelhardt (2013), provides the strongest evidence of significance of a change in electrical impedance myography (EIM) measurements with age. Uemura et al.'s, (2020) work linked a change in phase angle from whole body bioimpedance with change in older adults and risk of disability. Uemura et al., (2020) carried out a longitudinal study of over 4000 participants over the age of 65 and identified increased risk of disability at low phase angle (≤4.95° for men and ≤4.35° for women); they recommended its use in targeting supportive and preventative measures. Measurements from this study demonstrate a similar change in phase angle over a wider age range, but using a smaller cohort, demonstrating that the phase angle from EIM measurements could be used more widely. As described in **Section 1.7,** age as a parameter was used in this study to attempt to reflect the change of muscle tissue as it deteriorates. This study has identified that aging muscle has an increased impedance and could be used in the study of sarcopenia. This is supported by the literature (Hobson-Webb et al., 2018; Bourgeois et al., 2019; Tanaka et al., 2019).

Muscle is known to deteriorate with disease or disability. The use of EIM to monitor muscle health and predict the need for more intervention and support not only applies to people aging naturally but also to people with disabilities who may have need of intervention at an earlier age and cannot communicate it. EIM has also been applied to clinical trials and can be used to monitor disease progression in perhaps a less intrusive and more objective way.

Follow up of the participants would provide further information on the applicability of Uemura et al., (2020) to younger people. A study of patients with neurological conditions would also inform the use of phase angle measurements which could be measured using electrical impedance myography (EIM) easily and less intrusively than other measures.

4.3 Variation of electrical impedance myography (EIM) with gender

A statistically significant difference was seen in Zc and in phase angle between male and female participants. In all cases shown in **Table 3.15** the null hypothesis was rejected. This is a really interesting result. Initially it may be due to higher subcutaneous fat under the electrodes in women although the relative fat mass (RFM) (%) for men and women (**Table 3.7**) are very similar. Another possibility is that the gender variation seen was influenced by the age of the participants. The mean age of the women in the study was 50.42 ± 16.42 years, while for men it was 36.31 ± 13.99 years. As seen in **Section 4.2**, Zc was shown to increase with age. To further investigate this effect a larger sample across a wide age range or a larger sample of men and women in a smaller age range would need to be studied.

4.4 Variation of impedance with body fat percentage

Table 3.16 shows a significant Pearson correlation coefficient between Zc and body fat percentage but the regression coefficient is weak. The mean relative fat mass (RFM) (%) as described above is very similar for the men and women in the sample although the mean body mass index (BMI) for men is higher. Average calculated body fat percentage for women was 37.45% and for men was 24.91%.

On calculating the linear regression equation and correlation coefficient it was found to be strongest for female participants, $R^2 = 0.374$; for male participants $R^2 = 0.016$

indicating negligible correlation. However, Li, et al., (2016) found negligible variation between male and female subjects, but their study was slightly smaller (n = 23) and the age range of their healthy subjects was 23 to 46 years. They found that the highest variation factor was electrode orientation and distance between the electrodes.

Subcutaneous fat will increase the resistance to the electrical current and one way to overcome this would be to use needle electrodes. However, the use of needle electrodes would increase the risks associated with the test and reduce the patient acceptance of the test.

4.5 Limitations and confounders

It is recognised that there are limitations in this study and that there are ways in which it could be improved. Possible limitations and effects are discussed below.

4.5.1 Skin condition

It was noticed that for two volunteers the electrodes tended to peel despite skin preparation. The electrodes were secured using micropore tape to prevent loss of data during measurement. Peeling may have been due to excess sebum production. One of the volunteers had a medical history of psoriasis but electrodes were not attached over any plaques. All participants were asked after the measurements whether they had experienced any sensation in their arm during the measurements. Two participants, the youngest male and the youngest female, described a tingling sensation, but neither found it painful. No participants had excessive hair on their biceps and so none were shaved.

4.5.2 Blood flow and fatigue

Blood flow is possibly a minor contributor to Zc but given that the muscles were relaxed or in a partially active state the blood flow difference is thought to be minimal. The participants were asked to only slightly activate their muscles, there was no intention to cause muscle fatigue and no participant became fatigued during the short time of measurement. The biceps brachii muscle was only partially activated for less than two minutes; the IMP^{TM} SFB7 was very fast in making measurements. Fatigue is not considered to be a factor.

4.5.3 Hydration and exercise

All participants were requested not to drink for an hour before measurement. Excess hydration is considered to affect bioimpedance measurements which are generally used to calculate body water content (IMP^{TM} SFB7 guidelines for use). They were also requested not to perform excessive exercise before measurement. Excessive exercise such as running or going to the gym would increase blood flow and decrease hydration beyond the normal body status. Resistance from the extracellular and intracellular compartments would have been altered from their normal resting state in both cases so it was important to try to minimise these effects. Assuming all participants gave truthful answers at the measurement session these factors can be omitted.

4.5.4 Environment

The measurements were carried out at four separate locations due to COVID-19 pandemic restrictions. It was not possible to use the same location for all participants. In all locations the environment was kept as constant as possible to ensure that the participants were as relaxed as possible.

4.5.5 Electrode position

Positioning of the electrodes was done by palpation. The voltage, ‘sense’, electrodes placed at either end of the palpated muscle, the current source placed at the distal electrode, furthest from the shoulder and the current sink at the proximal electrode, closest to the shoulder as described in **Section 2.3** and shown in **Figure 2.3**.

The position of the electrodes was based on the individual’s biceps brachii anatomy and the ability to palpate this. As a result, the distance between the upper and lower dual electrodes varied between participants. Much work has been done on standardising electrode arrangements and the importance of electrode positioning, and Sanchez et al., (2016) demonstrate the variation in impedance measured if the electrode is moved only 7mm. The electrode method used here is subject to these errors, but this method was chosen since it is in closer agreement with the manufacturer’s instructions and fabrication of a specially constructed electrode arrangement, since none was commercially available, was beyond the scope of this work. Such an electrode would have measured impedance over a consistent length of muscle, but the method used here attempted to measure impedance over the length of the palpable muscle. Such an arrangement is more likely to mirror the practical arrangement advised by ImpediMed until a more appropriate electrode is available commercially. L. Li et al., (2016a) experimented with fixed position electrodes placed both longitudinally and transversally and were able to demonstrate different correlations with the bespoke electrode arrays. It is acknowledged that the electrode position may have had an impact on the measurements, and this is an area which could be improved.

4.5.6 Rest time between measurements

All participants were requested not to exercise excessively before measurement. They were all assessed and measured before the electrical impedance myography (EIM) measurements were carried out. They were seated and relaxed for a minimum of five minutes before commencing the EIM measurements. After each active cycle of the measurements they were all rested again for at least five minutes. Rest time and excessive activity are not considered to be a factor or confounder in the measurements of EIM.

4.6 Further discussion

As discussed, EIM has been shown to be an objective measurement technique and can indicate the health of the muscle; and it can be used passively, not requiring the person being measured to do anything. In this study it was found that the impedance of passive and active muscle was significantly different, so the null hypothesis was rejected. This was also true for the phase angle. However, an interesting consistency of ratio was seen between the two cycles of passive and active measurements: both in impedance and phase angle. To test whether this is a real phenomenon further cycles of passive and active testing would be needed. Should a consistent ratio be found to be statistically significantly then it may be possible to build on the first hypothesis; that is, that the impedance measurements of passive and active muscle, while not the same, may be linked by a mathematical function relationship.

It has been shown that impedance, Zc, and phase angle vary with age. This may be linked to studies of sarcopenia and muscle in people with a neuromuscular disease or disability, in which the muscle is not behaving as normal muscle. This enables this measurement technique to be clinically appropriate to wider patient groups, for

example patients with muscular dystrophy, multiple sclerosis, stroke and motor neurone disease.

The variation of EIM measurements, Zc and phase angle, with age has been interpreted as a change with declining muscle health. With a robust normal data set for Zc and phase angle it could be implied that EIM would be sensitive to muscle disease and may aid diagnosis; some studies have linked phase angle to the risk of falling in the elderly. Thereby it may aid clinical decision making.

It was interesting to note impedance measurements which may be considered outliers. One young male participant was measured with a higher impedance than was anticipated. This is thought to be due to the skin contact with the electrodes as discussed earlier. Two older male participants were measured with lower impedance values than were anticipated. Both are work colleagues and are very active for their age. However, when calculating phase angle one of the older female participants had a lower than expected phase angle. She also had the highest body mass index (BMI), and hence body fat percentage, which may have influenced the measurement.

In recruiting volunteers, this study was unable to recruit participants between 65 and 82 years old. Additional data here would have supported testing the hypotheses.

To further clinically develop this measurement technique larger clinical trials would be necessary. Initially clinical trials would need to collect data from a range of people without neurological conditions to establish a normal data set. This small study has demonstrated that Zc and phase angle vary with age and stronger statistical evidence is needed to establish the likely relationships between age and the data that can be collected. Variation with gender was seen in this small study and a larger

clinical trial would need to ensure a balanced range of participants. Further potential bias could also be investigated by ensuring the healthy adults in the larger clinical trial included people of different ethnicity and that skin condition over the muscles measured was accurately recorded to ensure that these confounding effects were considered. As already discussed, a greater number of cycles of passive and active measurements in a larger clinical trial could also provide statistical data to investigate the ratios seen here.

It is calculated that to increase the power of the study to 80% approximately 416 healthy participants would be needed. Ideally these would need to be evenly spread across the adult age ranges and genders, with approximately 70 participants in each age range. The use of age ranges was seen to help approximate a complex issue and when only two age ranges were used greater clarity was seen.

Having established a normal data set clinical trials across different groups of patients with neurological conditions would be expected to provide data, Zc and phase angle, for comparison with the normal data. Given that the technique is passive it also makes it a more inclusive measurement technique, available to those who cannot move their muscles voluntarily.

The sensitivity and specificity of the technique of measuring impedance and phase angle would be tested further in much larger clinical trials.

As discussed in section 4.5.5, it is likely that the biggest factor in the accuracy of the measurements is the placement of the electrodes. Whilst it has been seen in the literature that bespoke fixed electrode arrays can be used, these were not part of the medical device in use. It was beyond the scope of this work to develop and use a fixed array; indeed, if the IMP^{TM} SFB7 device is to be recommended for clinical and

community use it needs to be usable as supplied. An electrode array available commercially would strengthen it being recommended for widespread clinical use. The main reason for this being that very careful measurements are not easy to make accurately in the community. The simpler the device is to use accurately the greater its acceptance would be; this is demonstrated by the use of manual muscle testing and hand-held dynamometers.

The IMP^{TM} SFB7 was easy to set up and use and could be used in both clinical and community settings, its accuracy would be enhanced by a fixed electrode array to negate varying electrode placement. It also provides a more objective measurement of muscles, and measurements here and in the literature demonstrate that it can distinguish changes of muscle with age, and therefore potentially with degradation due to disease and neurological conditions.

5 Conclusion and further work

This study has met its aims and explored the question ‘Can electrical impedance measurements of muscles be used to assess muscle health?’ using four research questions to test the hypotheses. This work has demonstrated that with healthy volunteers there is a difference in impedance and phase angle with age and gender. The impedance and phase angle also differ between active and passive muscle. These relationships could be further explored with a much larger cohort of participants in an even wider, and more evenly spaced, age range as described in **Section 4**. The difference in impedance and phase angle detected between male and female participants could also be investigated in studies where a balanced number of male and female participants in each age group were enrolled. The work would provide a further baseline for comparisons of healthy and diseased muscle. This could be used clinically to allow greater comparison with patients exhibiting sarcopenia, to detect changes in patients with neurological conditions and to make clinical decisions such as whether a patient has sufficient muscle strength to use a mobile arm support, as per the clinical innovation proposal in **Appendix 5**.

More work to investigate the ratio of active and passive muscle impedance may also reveal stronger relationships as described earlier. Some researchers have used a fixed shaped arrangement of the electrodes on the belly of the muscle thereby eliminating any variation in distance between the electrodes. Development of a fixed shape arrangement of electrodes may reduce measurement errors. Repeated recordings of muscle impedance in a timed cohort study would enhance knowledge in this area.

The muscle activity used in this study was designed to be simple and not cause the participant fatigue, however, more work exploring greater muscle activity would provide more information. The measurement of impedance during daily living tasks would improve the applicability of the research. This can sometimes be difficult to model since when asked to perform an action, such as lifting a cup, patients with impaired muscle function may find a way to compromise how they do the task if it cannot be achieved by the usual muscles. The muscles measured may not be the ones that are doing most of the work.

The use of electrical impedance myography (EIM) and measurement of impedance has the potential to inform clinical decision making in mobile arm support assessment. Many other areas where muscle health assessment is needed to support clinical diagnosis would be supported by electrical impedance measurements especially if the medical device were easy to use and interpret. EIM has been found to have a wide variety of applications; it can be used to measure tissue in pressure area investigations to indicate if the tissue damage is greater than the surface suggests (Swisher et al, 2015), and it has been used as a biomarker in clinical trials (Turner et al., 2013). It is a more acceptable test for patients since it can be done passively, this may make it more acceptable psychologically since the patient may not feel that they have ‘failed’ the measurement or test. The technique also does not require needles, which improves its acceptance and infection risk; it is also portable and easy to use. It can potentially be accessible to a much wider range of patients than other methods, since it does not require movement of the muscles. This is seen as an advantage since it could have application in the intensive care environment as well as with patients who cannot move their muscles voluntarily, for example if they have cerebral palsy, or move their muscles due to a neurological

condition. As Sanchez and Rutkove (2017) conclude ‘EIM will gradually be adopted into the standard repertoire of neuromuscular assessment tools’. As the clinical evidence base grows and the technology becomes easier to use accurately it is envisaged that EIM will take its place alongside other established techniques such as electromyography and nerve conduction testing. It is much less expensive than MRI and other whole body scanning techniques. EIM has the flexibility to be used both in a hospital clinic setting as well as in the community which adds to its value as we move towards more community healthcare and ‘hospital at home’, improving patient care and efficiency of health care.

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Appendix 1 Simple literature search: upper and lower limbs

'Biomechanics', 'gait', 'arm' and 'upper limb' search table

Table A1.1 Search criteria in Cardiff University library

Any field	Any field	Title	Hits	Comments
Biomechanics	gait		8098	
Biomechanics	arm		6598	
Biomechanics	upper limb		3582	
Biomechanics		gait	2339	
Biomechanics		arm	184	(some relate to gait)
Biomechanics		upper limb	156	

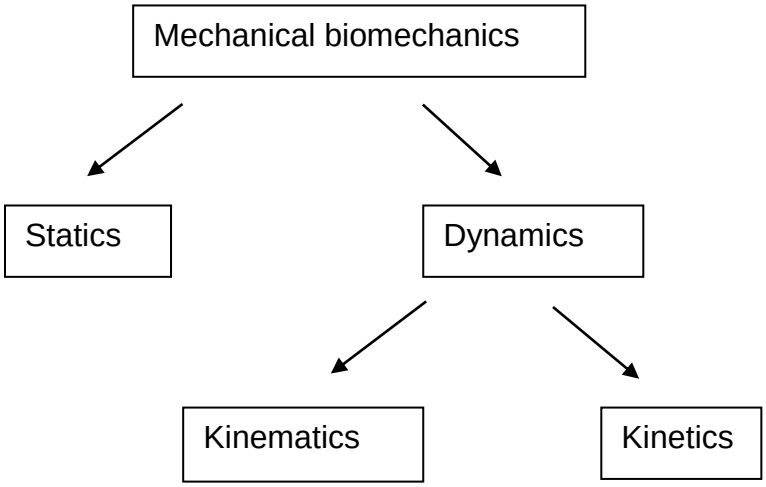
Appendix 2 Brief outline of kinesiology, biomechanics and kinematics

A2.1 Basic understanding of Kinesiology, biomechanics and kinematics

Kinesiology is the study of human motion (Mansfield and Neumann, 2009, p. 2; Lippert, 2006, p.1; Luttgens et al., 1992, p. xiii). Lippert (2006, p.1) describes kinesiology as bringing together the fields of 'anatomy, physiology, physics and geometry' as related to human movement, perhaps better described as human kinesiology. Klette and Tee (2008, p.22) consider that kinesiology and biomechanics are 'basically identical'. This seems erroneous given that the definition implies that biomechanics is a branch of kinesiology. However, more caution must be given to the term Applied Kinesiology which is a form of alternative medicine (Barrett, 2003).

Biomechanics is the study of the mechanics of life (Cerny, 1984) and is described as a branch of kinesiology. The relationship is seen below.

Figure A2.1 – from Basic Biomechanics (MOTT, 2019) and adapted



Kinematics describes the motion of the body without reference to the forces. Kinetics examines the forces acting on the body during motion with respect to time and forces.

A2.2 Biomechanics

Tarata (2003) clearly describes the two mechanisms that produce a voluntary muscular force: the firing frequency and the recruitment of muscle motor units. When a muscle contracts a complex series of processes takes place (Lorenz and Campello, 2012, p.151).

The motor unit is the functional unit of skeletal muscle (p155). A motor unit consists of a motor neurone and all of the muscle fibres it innervates. When a signal stimulates it, all of the muscle fibres attached to the motor neurone contract maximally as one unit; it is the smallest unit which can contract independently. The size of the muscle is generally related to the fineness of the movement it produces and the number of muscle fibres in the motor unit. Lorenz and Campello (2012, p.155) describe how in fine ocular muscles each motor unit may contain less than 12 muscle fibres whereas the gastrocnemius (calf muscle) motor units may contain between one and two thousand. Although the motor units contract maximally when stimulated they are interspersed amongst other muscle fibres which are part of different motor units. If greater contraction is required more motor units are activated to produce a greater force. This is called recruitment.

Electromyography (EMG) has been a very important tool for investigation of the neural effects on muscle and its activity (Lorenz and Campello, 2012, p.158), the

contractile process and the time relationship between stimulus and activity. Twitch is the mechanical response of a muscle to stimulus of its motor nerve, which should, from the previous definition of a motor unit, be a full contraction of that motor unit. The time from stimulus to the start of contraction is called the latency period, the time to full contraction or peak contraction is the contraction time and the time from full contraction back to zero tension is the relaxation time. The speed of contraction and relaxation is dependent on the muscle fibre type. The initial stimulus of the motor neurone, called the action potential, is only 1 or 2 milliseconds so it is possible for additional stimuli to be applied to the muscle before the initial one has completed the contraction-relaxation cycle. When this happens the tension in the muscle is greater than following a single stimulus and when muscle tension is under maximum summation of activated potentials the muscle is said to be in tetanic contraction.

Voluntary muscles are generally seen to contract in a controllable manner and this is thought to be due to differential action potentials on the motor units in the muscle under observation producing activation in a co-ordinated way to produce a controlled and smooth contraction.

Muscle fatigue depends on the availability of adenosine triphosphate (ATP) which has been described as the ‘molecular currency of intracellular energy transfer’ (World of Molecules, 2018). If muscle activation is continued and contraction frequency is slower than the synthesis of ATP in the muscle, then the contraction can continue for a long time. Lorenz and Campello (2012, p.166) describe three sources of ATP production.

Lorenz and Campello (2012, p.168) identify three different types of muscle fibres, distinguished mainly by the metabolic pathways in which they generate ATP and the

rate at which its energy is made available to the muscle unit which in turn determines the speed of contraction. This is summarised in **Table A2.1.**

Table A2.1 Summary of muscle types and properties

Type 1 red fibres slow twitch oxidative (SO).	Very difficult to fatigue because rich blood supply and nutrients allow sufficient synthesis of ATP to meet slow twitch demands. Small diameter, little tension. High myoglobin – red colour.	Prolonged, low intensity work.	Ocular, finger, face, note:– chickens have mostly type 1 slow twitch in their legs and they do a lot of standing and walking and don't get fatigued. However, their breast meat is white, fast twitch, so does not have so much blood, but is ready for quick flight.
Type IIa: fast twitch oxidative-glycolytic (FOG) red fibres intermediate between type I and type IIb.	Fast contraction time aerobic and anaerobic activity, well developed blood supply – can maintain activity relatively long – often categorised as red muscle.		
Type IIb: fast twitch glycolytic (FG) white fibres.	Low blood supply, relies on anaerobic activity for ATP production.	Fatigues very easily – generally large diameter and able to produce high tension for short periods before fatigue.	Eg sprinting muscles or chicken wings.

Lorenz and Campello (2003) describe how the nerves innervating a muscle unit determine its type (Burke et al., 1971), thus as described above muscle fibres of a muscle unit are all one type and that type is determined by the nerve.

Fibre composition depends on the function of the muscle, muscles that perform one type of activity are predominantly composed of one type of fibre. More commonly activity is mixed and therefore so is fibre type.

Elite athletes trained in endurance sports are found to have 80% type 1 muscle; athletes trained in short explosive sports have 30% type 1. However, it is generally accepted that fibre type is genetically determined but fibre type can be determined by nerve so there may be some cortical control.

Disuse and immobilisation have a detrimental effect on muscle fibres (Lorenz and Campello, 2003, pp.169-170). It is found that it is mainly type 1 fibres that atrophy with immobilisation, which also results in a reduction in cross-sectional area. Disuse changes the biomechanical properties on many levels.

Table A2.2 from Harrison (2018)

Characteristic	Type I	Type IIA	Type IIX / IIB
Contraction time	Slow	Fast	Very fast
Size of motor neuron	Small	Large	Very large
Resistance to fatigue	High	Intermediate	Low
Activity used for	Aerobic	Long term anaerobic	Short term anaerobic
Force production	Low	High	Very high
Mitochondrial density	High	High	Low
Capillary density	High	Intermediate	Low
Oxidative capacity	High	High	Low
Glycolytic capacity	Low	High	High
Major storage fuel	Triglycerides	CP, Glycogen	CP, Glycogen

A2.3 Kinematics

The kinematics of arm movement are complex and are considered more complex than gait movement because of the much wider range of movement (ROM) of the shoulder joint, elbow joint and the wrist and hands (Gates et al., 2016; Veeger and Nikooyan, 2011). Kinematics has the potential to inform clinical decision making but progress on analysis is slow due to its complexity. Gates et al., (2016) provide a comprehensive but brief analysis of the attempts to link kinematics of arm movement

to activities for daily living (ADL). They conclude that there is no single method used for joint angle, which makes comparisons difficult. Different research groups have looked at limited joint movement or a limited range of ADL, again making it difficult to compare. Concerned about the lack of evidence in measurements of ADL, Hawkes et al., (2011) investigated the co-ordination of muscles in the shoulder during movement undertaken in a shelf-lifting exercise in the FIT-HaNSA testing regime (MacDermid et al., 2007) using electromyography (EMG). They demonstrated that a wider range of muscles are used in upper limb activities than previously thought and that this was important to understanding upper limb activities.

To improve consistency of joint measurement, both inter-tester and intra-tester, Norkin and White (1995) recommend that:

- Use consistent, well defined test positions and landmarks.
- The same amount of force should be applied to move the body segment in the assessment of the passive range of movement.
- Subjects should be encouraged to exert the same effort to perform a movement in the assessment of the active range.
- Repeated measurements should be taken with the same measuring device to reduce the variability of measurement.
- Where possible successive measurements should be taken by the same examiner.

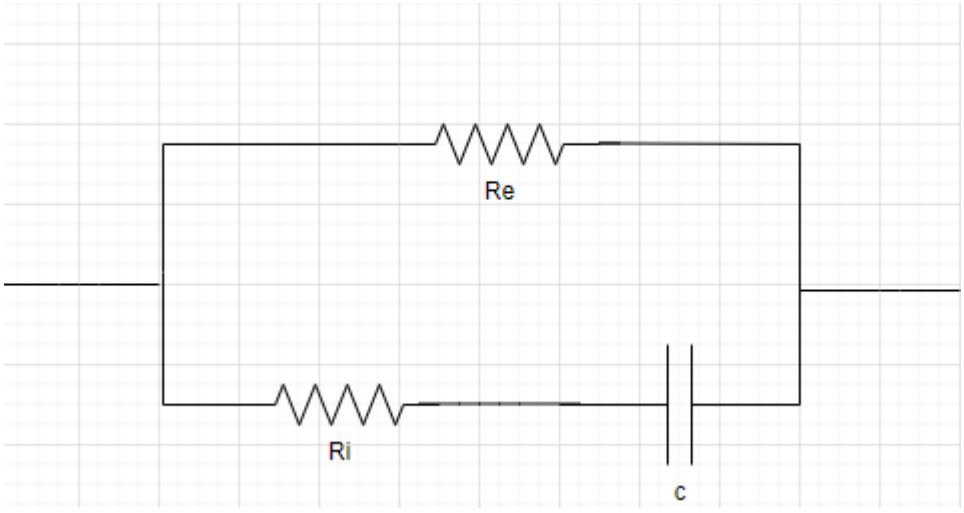
Appendix 3 Electrical Impedance Myography: Background and Physics

An introduction to bioimpedance and electrical impedance myography is well covered in the literature (Holder, 2004; Khalil et al., 2014; Bartels et al., 2015; Cebrian-Ponse et al., 2021), but this appendix provides a short summary.

Bioimpedance refers to the electrical properties of biological tissue when subject to electrical current. An opposition to the current is a property called resistance if the current only moves in one direction (Direct Current, DC) and impedance if the current moves backwards and forwards (Alternating Current, AC). In an AC circuit there may be resistive and reactive components making up the overall opposition to the current, the impedance. The reactive components may be capacitive, or inductive, both of which store and resist electrical charge but in different ways and alter the phase of the AC. The phase refers to the AC wave form (usually sinusoidal) of the current and voltage not coinciding, one will lead the other depending on the components of the circuit. The existence of a phase difference means that equations to calculate AC properties need to include complex numbers, j.

One of the simplest circuits to model current flow in tissue is shown in **Figure A3.1** as described by many authors including Cornish et al., (1993) and Holder (2004).

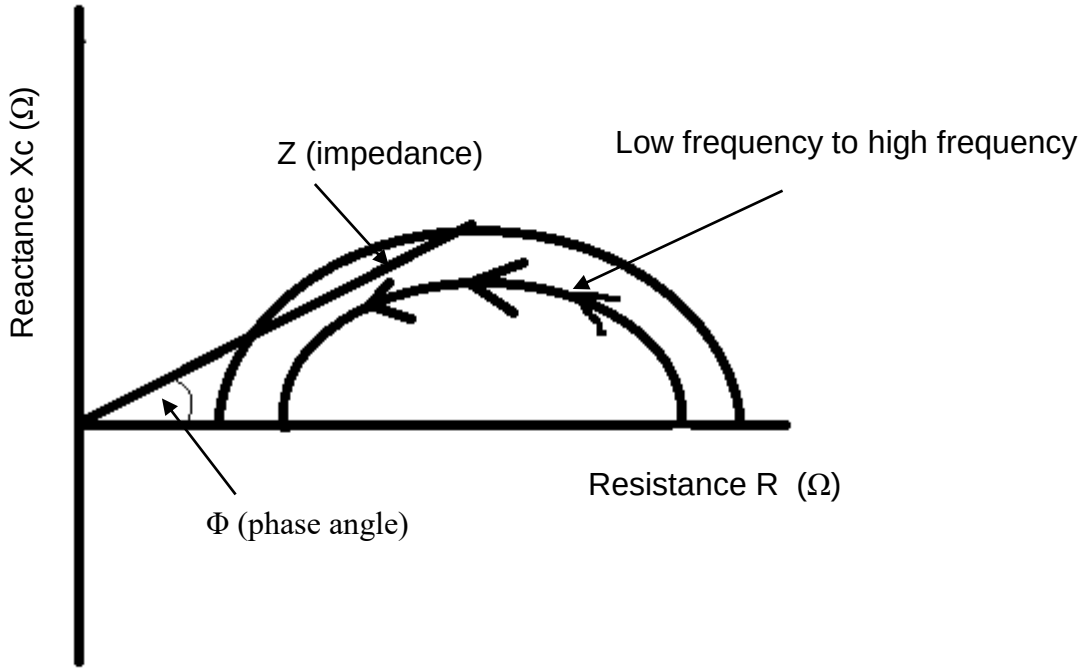
Figure A3.1 Bioimpedance basic circuit after Holder (2004)



From Holder (2004). Where Re = extracellular space resistance. Ri = intracellular space resistance, C = capacitance

The change of resistance and reactance with frequency is shown in **Figure A3.2.** Reactance here is denoted by Xc since from the circuit in **Figure A3.1** it is only the capacitor which is a reactive component, so the ‘c’ refers to the capacitance effect. Biological tissue contains salt ions and is highly conductive, however, the salt ions are held both intracellularly and extracellularly and have the cell membrane dividing them. The cell membrane acts as a capacitor. At low frequency (toward the right in **Figure A3.2**) the resistance is high because the current flow through the extracellular salt ions and consequently the impedance is mostly resistive, this is Re, extracellular space resistance. At higher frequencies the current can cross the capacitance of the cell membrane and also flow through the intracellular salt ions, this is Ri, the intracellular space resistance, resulting in a lower impedance.

Figure A3.2 Impedance locus for the circuit in figure A3.1 after Cornish et al., (1993): Cole-Cole plot



Impedance is a measure of the opposition of the tissue to the flow of electrical current. Since tissue is a complex material its 'opposition' to current flow is given by

Equation 1

Impedance (Z) = Resistance (R) + Reactance j(Xc) **Equation 1**

Where j indicates an imaginary number symbolising the complexity.

Reactance = $\frac{1}{2\pi f c}$ **Equation 2**

Resistance = $\frac{V}{I}$ **Equation 3**

Where f= frequency (Hz), c= capacitance (farads) V= voltage (volts) and I = current in amps.

$$|Z| = \sqrt{R^2 + Xc^2}$$ **Equation 4**

$$\Phi = \tan^{-1}\left(\frac{Xc}{R}\right)$$ **Equation 5**

Where Φ is the phase angle between the reactance (Xc) and the resistance R – see **Figure A3.2**

The frequency at the peak of the Cole-Cole plot is called the characteristic frequency. At this point the reactance, Xc, is at a maximum, and it is at this point that the maximum contribution of the capacitive effect of the cell membrane is seen. It is also the point at which the current is equally divided between the extracellular and intracellular compartments (Foster and Schwan, 1989; Sanchez and Rutkove, 2017). Cornish et al., (1993) argue that the characteristic frequency is needed for predicting body water from the impedance and that this cannot be done from a predetermined frequency since the capacitance must be accounted for. The impedance at the characteristic frequency is therefore used in the calculations and is part of the reported data from the multifrequency bioimpedance meter.

Appendix 4 Clinical Trial

A4.1 University of Manchester form

DCLINSCI C RESEARCH PROJECT PRO FORMA

Completed forms should be emailed to:

Physiological Sciences/Life Sciences - DClinSci@manchester.ac.uk **OR**

Physical Sciences/CBE – PhysSci.DClinSci@manchester.ac.uk

Trainee Details	
Name:	Stephanie Wentworth
Student ID:	10105668
University:	University of Manchester
HSST Specialism:	Clinical Biomedical Engineering
Place of work:	Cardiff and Vale University Health Board
Date proforma submitted:	14/08/2018

Research Project Details	
Research dissertation working title:	An investigation into finding an objective measure of arm muscle strength

Name of proposed workplace supervisor:	Professor Colin Gibson
Contact email of proposed workplace supervisor:	Colin.Gibson@Wales.nhs.uk

Description of proposed research (500 words maximum)

Please include:

(a) Aims of the research

To research and develop a reproducible objective measure of arm strength

(b) Principal research question(s)

1. Arm strength is a measure which can be monitored in neurodegenerative disorders and rehabilitation programmes; is there an objective measure of arm strength that can be used in the clinical and community environment?
2. Can electrical impedance myography (EIM), which has been identified as a non-invasive biomarker be used routinely to monitor arm strength?

(c) Proposed methods

Investigate and critically analyse existing methods of clinical arm strength assessment. Investigate the forces required for effective arm movement for activities of daily living (e.g. feeding and grooming). Investigate and test the optimal use of electromyography

(EMG) and EIM as a measure of muscle activity and related to arm strength in the clinical and community environment.
(d) Potential impact of research An objective measure of arm strength will provide reproducibility of measurements for health care professionals who provide rehabilitation and monitor neurodegenerative conditions which affect arm movement. Current measures are subjective, relying on health care professionals developing highly specialized skills to manually gauge arm strength and their ability to convey the results in a reproducible way.
(e) A summary of patient and public involvement in the research This work may collect clinical user opinions of existing and proposed measures of arm strength.

Research Governance	Yes:	No:
(a) Does your proposal involve animal experimentation? If yes, do you and/or your proposed supervisor hold a valid and current animal licence? (please give details)	☐	☒

Research Governance	Yes:	No:
Click here to enter text.		
(b) Does your proposal involve human participants?	☒	☐
(c) Does your proposal involve samples covered under the Human Tissue Act (HTA)?	☐	☒
If you answered yes to either (b) or (c) above; • Is ethical approval required? • If required, has ethical approval been obtained? (please give details) Unsure if it will be required	☐ ☐	☐ ☐

Research Costings	Yes:	No:
(a) Has the project been costed?	☒	☐
(b) Are funds in place to cover the costs? If funds are not in place, outline the approach to securing these costs: Click here to enter text.	☒	☐

Research Costings	Yes:	No:

For Office Use Only:

Approval of C2 Research Project by University	
HSST Lead:	Select HSST Lead from list.
Notes:	Click here to enter text.
Signed:	
Date approved:	Click here to enter text.

Approval of C2 Research Project by Royal College of Pathologists (Life Sciences only)	
Name:	Click here to enter text.
Notes:	Click here to enter text.
Signed:	
Date approved:	Click here to enter text.

A4.2 Cardiff and Vale UHB R&D Cardiff and Vale UHB R&D Sponsorship request form

RESEARCH AND DEVELOPMENT OFFICE

Sponsorship Request Form

This form must be completed for all **requests for the UHB to act as Sponsor**

Please refer to Applying for Cardiff and Vale UHB Sponsorship SOP SR-RG-018 prior to completion.
Please ensure all information requested is provided.

Please submit this form to:	Research.governance@wales.nhs.uk

Please include the following in the email subject:	Sponsorship Request
If already available, please provide the following:	Draft protocol Draft participant information sheet Draft consent form Grant Information (if applicable)

SECTION 1:

Study Title:	**An investigation into an objective measure of muscle quality, function and ability**
Chief Investigator **Please include name + email & postal contact details.** *This is the person with overall responsibility for the study*	Dr Stephanie Wentworth Stephanie.wentworth@wales.nhs.uk Stephanie.wentworth@postgrad.manchester.ac.uk Rehabilitation Engineering Unit Artificial Limb and Appliance Service (ALAS)

	Cardiff and Vale University Local Health Board Posture and Mobility Centre Unit A, Bridge Road, Treforest Industrial Estate, Treforest, CF37 5TF
Chief Investigator's substantive employer:	Cardiff and Vale UHB
Directorate & Clinical Board:	ALAS SS
Trial Manager (if applicable)	

SECTION 2:

Please note that if your study meets any of the criteria below, it is unlikely that C&V UHB is able to sponsor.

If you tick yes to any of the criteria, it is recommended that you contact R&D to discuss further before proceeding with the rest of this form.

Criteria	**Yes**	**No**
Phase 1 CTIMP study involving healthy volunteers	☐	X☐

Study includes sites outside UK	☐	X☐
Commercial contract research	☐	X☐
The Chief Investigator is neither employed by, nor holds an honorary contract with C&V UHB	☐	X☐
Study undertaken as part of an academic qualification	X☐	☐

As discussed with R&D, please see attached emails

SECTION 3:

Has funding been obtained?	**Yes** ☐X – part of the HSST training funding. There are no other costs to C&VUHB **No** ☐
	If yes, please provide details: part of the HSST training funding. There are no other costs to C&VUHB
	If no, please provide details of how the study will be funded:
	Yes ☐X

Will any part of this study contribute to an educational qualification?	**No** ☐
	If yes, please provide details* of course & course supervisors (name + email address)*: the DClinSci part of the HSST programme. Please see emails to R&D attached. Higher Specialist Scientist Training Programme, National School of Healthcare Science incorporating PGDip in Leadership and Management in Healthcare Science, Higher scientist training and DClinSCi. Provided by a consortium of universities; I am registered with University of Manchester and Liverpool University for my speciality of Clinical Biomedical Engineering. ***Local supervisor Prof Colin Gibson*** ***Consultant Clinical Scientist*** ***Colin.Gibson@Wales.nhs.uk*** ***Academic Supervisor Prof Tony Fisher,*** ***Consultant Clinical Scientist, Royal Liverpool University Hospital*** ***A.C.Fisher@Liverpool.ac.uk***

Anticipated start date of recruitment	January 2020
Anticipated end date of recruitment	June 2020
Length of patient follow-up	Not applicable: measurements will take place only once.
How many patients do you intend to recruit in total?	Approximately 20 healthy volunteers
How many sites involved?	one
Is the study interventional?	**Yes** ☐ **No** ☐X
	If yes, please provide details of the intervention:
Does the study involve an Investigational Medicinal Product (IMP) and/or Device?	**Yes** ☐ **No** ☐X
	If yes:

	Please provide details of the IMP/Device:
	***IMP/Device* provider**
	Study phase (IMP) or CE marking status (Device): CE marked device to be used
Will any third parties be involved (e.g. Clinical Trial Units, or other service provider) at any stage of the research (e.g. management, supplies, sample processing etc):	**Yes** ☐ **No** ☐X
	If yes, please provide details:
Has the study undergone scientific/peer review?	**Yes** ☐X A literature review has been written and reviewed by my supervisors. They have provided comments which will be acted on and it has been passed and recorded as approved on the Manchester research project software eprog. **If Yes- please provide evidence with request for Sponsorship** A literature review has been written and reviewed by my supervisors. They have provided

	comments which will be acted on and it has been passed and recorded as approved on the Manchester research project software eprog. **No** ☐
Will any computer systems be used for managing study data (e.g. databases, spreadsheets, bespoke software):	**Yes** ☐X **No** ☐
	If yes, please provide details: Software for analysis forms part of the device and the device is CE marked as a medical device. Further analysis will be done in Excel.
Does the Chief Investigator or any other member of the research team have any conflict of interest?	**Yes** ☐ ***If yes, please provide details:*** **No** ☐X
Has the study been discussed with your Directorate R&D Lead to ensure it fits within the Directorate/Clinical Board strategy?	**Yes** ☐X **No** ☐

Name of Directorate R&D Lead	Prof Colin Gibson

NOTE:

For research that C&V UHB subsequently agrees to sponsor, the following will apply:

- The Chief Investigator will have overall responsibility for ensuring that the study is conducted in accordance with all applicable regulations and in accordance with C&V SOP Applying for Cardiff and Vale University Health Board Sponsorship SOP available on the C&V UHB intranet pages.
- The Chief Investigator must agree to the C&V UHB Terms & Conditions of Sponsorship and to accept their delegated responsibilities.
- The Chief Investigator will be accountable to the Sponsor.
- Sponsorship may be withdrawn where the Chief Investigator fails to comply with the C&V UHB Terms & Conditions of Sponsorship.

Must be signed by the Chief Investigator.

Signed:	
Name: (PLEASE PRINT)	Stephanie Wentworth
Date:	12/8/19

FOR R&D OFFICE USE ONLY	
Suitable for consideration?	Yes
Likely to fall under simple or complex definition during risk assessment?	Simple
Current versions of all Cardiff and Vale Research SOPs and accompanying documents are available electronically. If you are reading this document in printed form, please check that the version number and date match the most recent version on the Research & Development intranet pages.	
Outcome relayed to CI:	On 06/11/19

A4.3 Clinical Trial Protocol

Protocol V1.1

Full title

An investigation into an objective measure of muscle quality, function and ability.

Sponsor: Cardiff and Vale University Health Board, University Hospital of Wales, Heath Park, Cardiff, CF14 4XW Tel. 029 2074 7747

Study Coordination Centre: Rehabilitation Engineering Unit, ALAS Posture and Mobility Centre, Treforest, CF37 5TF
Funder: This study forms part of the NSHCS Higher Specialist Scientist Training (HSST) programme.
Chief Investigator: Stephanie Wentworth, Rehabilitation Engineering Unit, ALAS Posture and Mobility Centre, Cardiff and Vale University Health Board, Treforest, CF37 5TF
R&D ref: 7703
REC ref:
IRAS ref: 266115
Protocol version number and date: Version 1 dated 10/01/2020

This protocol has been authorised by:

Name	Role	Signature	Date
Stephanie Wentworth	Chief Investigator		

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GENERAL INFORMATION

1.1 Study Summary

Study Title	An investigation into an objective measure of muscle quality, function and ability
Internal ref. no.	7703
Study Design	Observational cohort of healthy volunteers.
Planned Sample Size	20
Planned Study Duration	Recruitment will last six months from the study opening. Study end date August 2021.
Primary Objectives	To test whether electrical impedance myography (EIM) can be used as an objective measure of muscle ability.
Secondary Objectives	To test two hypotheses:

	The EIM measurement of passive and active muscle is not significantly different. EIM measurements in younger and older adult volunteers is significantly different.
Statistical Methodology and Analysis	Electrical impedance is being measured in two situations with each participant. These measurements can then be analysed with regard to each other and also with regard to the volunteer's age, physical health (perceived and measured with BMI and RFM). A T-test analysis will be used in the analysis.

1.2 Funding and Support in kind

FUNDER(S)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Cardiff and Vale University Health Board	**Sponsor**
University of Manchester and University of Liverpool	**This study forms part of the NSHCS Higher Specialist Scientist Training (HSST) programme.**

1.3 Role of Study Sponsor and Funder

The study forms part of the NSHCS Higher Specialist Scientist Training (HSST) programme. This programme requires the completion of a DClinSci; for the CIs specialism, Clinical Biomedical Engineering, this is jointly supported through the University of Manchester, the University of Liverpool and Cardiff and Vale University Health Board as the employing health organisation. C&VUHB have agreed to support my HSST study as part of the contract with NSHCS and HEIW. Other contributors will be acknowledged.

1.4 Protocol Contributors

University of Manchester (the study is registered for a DClinSci)

Liverpool University (the academic supervisor's organisation)

Cardiff and Vale University Health Board (the researcher's organisation employer and local supervisor's organisation)

ABBREVIATIONS

ADL	Activities of daily living
BMI	Body Mass Index
CI	Chief Investigator

C&V UHB	Cardiff and Vale University Health Board
CRF	Case Report Form
DClinSci	Doctor of Clinical Science
EIM	Electrical Impedance Myography
EMG	Electromyography
GCP	Good Clinical Practice
ISF	Investigator Site File
HCRW	Health and Care Research Wales
HEIW	Health Education and Improvement Wales
HRA	Health Research Authority
MAS	Mobile arm supports
NSHCS	National School of Healthcare Science
NHS	National Health Service
PI	Principal Investigator
R&D	Research & Development
REC	Research Ethics Committee
RE	Cardiff Rehabilitation Engineering
RFM	Relative Fat Mass
SOP	Standard Operating Procedure
TMF	Trial Master File

BACKGROUND AND RATIONALE

Rationale

The assessment of muscular function, quality and ability is of high importance in a diverse range of clinical disciplines from anaesthetics to physiotherapy. This study will look at the range of measurement techniques currently in use and development and considers their effectiveness and objectivity. It will also investigate whether an objective measurement technique can be found or developed that can be used both in the clinical environment and the community setting. This will focus on upper limb function and ability; ability is used here instead of strength since ability better describes functions needed for daily living rather than the maximum output a muscle is capable of.

This study developed from a need to assess arm muscles in patients who had been referred to Cardiff Rehabilitation Engineering (RE) for mechanical mobile arm supports (MAS). MAS are designed to support arm weakness and are a device to assist activities of daily living (ADL). They can be used to assist feeding and drinking, using a keyboard or even turning the pages of a book. They can also be used in rehabilitation programmes and to assist in maintaining range of arm movement in patients at risk of contractures and other movement limiting conditions. In assessing patient arm function in their homes, it became apparent that manual muscle testing was not objective and was an inadequate measure of success with a MAS; motivation for independence and good local support were better indicators. Notwithstanding the above interest was piqued regarding how muscle function could

be measured objectively and reliably in all healthcare settings, including the patient's home.

Background

Analysis of upper arm movement and the forces involved has long been studied in biomechanics, although it has tended to take second place to gait analysis (Anglin and Wyss, 2000; Buckley et al., 1996; Nordin and Frankel, 2012). The literature review (available on request) contains a brief outline of kinesiology, biomechanics and kinematics and raises some of the ongoing queries, for example whether or not there is a standardised scale for clinical movement: Anglin and Wyss (2000, p.542), discuss how there are no standard activities in comparison to gait and that none, at that point in time, could be recommended. Veeger and Nikooyan (2011) produced an online interactive document to share practice on shoulder measurement protocols demonstrating that there was no agreed practice at that time.

Leaving aside clinical motion measurement and concentrating on the muscles used for the motion it has become apparent that there are many inconsistencies in measuring muscle ability, function, force and quality because of the complexity of the process of muscles moving the body (Buckley et al., 1996; Merlini, 2010). The biochemical process of powering the muscle is highly complex and the rate at which the energy is used defines the fatiguability of the muscles. The actual muscle fibres are grouped into motor units activated by a single motor neurone and are either at rest, in the process of contraction or fully contracted; they cannot be sustained or rendered into a state of partial contraction. This gives a 'digital' feel to muscle contraction. Motor units may also consist of only a few muscle fibres (Norkin and Frankel, 2012), allowing very fine muscle control such as around the eyes, or they

may consist of thousands of muscle fibres such as in the large motion muscles of the legs. All of these factors complicate muscle activity measurement.

From this background the literature review (available on request) explores what can be measured, the problems of measurement and its objectivity. The aim is to investigate whether there is a method of measuring muscle quality, function and ability that can be used objectively in the clinical environment or the community with equal ease or whether such a method can be developed.

The literature review identified electrical impedance myography (EIM) as a potentially objective technique to measure muscle quality and ability. Two hypotheses are proposed:

The EIM measurement of passive and active muscle is not significantly different.

EIM measurements in younger and older adult volunteers is significantly different.

OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Objectives	**Outcome Measures/Endpoints**
Primary Objective To investigate EIM as an objective measure of muscle quality, function and ability	Using healthy volunteer measurement of EIM in arm muscles when relaxed and contracted.

Secondary Objectives The EIM measurement of passive and active muscle is not significantly different. EIM measurements in younger and older adult volunteers is significantly different.	Measurements taken on healthy volunteers will be used to test the two hypotheses

STUDY DESIGN

The investigation method used will be EIM as identified in the literature review.

The research design is both observational and experimental. The primary aim is to test whether EIM can be used as an objective measure of muscle quality, function and ability.

The hypotheses:

The EIM measurement of passive and active muscle is not significantly different.

EIM measurements in younger and older adult volunteers is significantly different.

Hypothesis 1: this is experimental. EIM is measured on an arm muscle when relaxed and then the muscle is activated and it is measured again. Each participant will be asked to consent to the same set of measurements, there will be only one set of measurements taken on each subject. There will be no recall for further measurements.

Hypothesis 2: this is observational. EIM measurements will be compared to age.

Other data variables will be collected and may be used in the analysis as weighting factors and to address confounding factors such as fitness level and general body composition, e.g. Body Mass Index (BMI) and Relative Fat Mass (RFM).

STUDY MANAGEMENT

The study will be undertaken by the Chief Investigator (CI) Dr Stephanie Wentworth, Clinical Scientist, as part of the DClinSci section of the Higher Specialist Scientist Training (HSST) programme. The two research supervisors are Professor Colin Gibson (C&VUHB) and Professor Tony Fisher (University of Liverpool).

The CI will meet with both supervisors on at least a bi-monthly basis, by either teleconference or in person to discuss the progress of the study and any issues arising. All progress will be recorded using eprog with Manchester University.

SCHEDULE OF STUDY PROCEDURES

Procedures	**Visit 1**
Eligibility assessment through screening	X
Medical history	X
Informed consent	X
Demographics (age, height, weight, waist size)	X
Physical examination for placement of electrodes	X
Assessment 1 Relaxed EIM	X
Assessment 2 Muscle contracted EIM	X
Adverse event assessments	X

PARTICIPANT IDENTIFICATION

Study Participants

It is intended that 20 healthy volunteer participants will be recruited over a period of six months.

Inclusion Criteria

Participants will

be volunteers

be over the age of 18

no pre-existing neuromuscular disease

not have an implanted cardiac device

be well at the time of measurement

be able to give informed consent

Exclusion Criteria

Participants will not have:

Any existing neuromuscular disorder (e.g. multiple sclerosis, ALS, MND, CP)

Any existing cardiac disease (including having a pacemaker or ICD)

Active arthritis

Be pregnant

Any other implanted electrical device

Not able to give informed consent

STUDY PROCEDURES

Recruitment

Only the CI will be involved in recruitment and measurements.

Participants will be recruited through an advertising campaign within the local area using a poster campaign. Participants will be able to email the CI for information on the study and express their interest.

Participants will be given or sent a copy of the patient information sheet (PIS). When they have read this and are interested in participating in the study they are invited to contact the CI using the contact details on the PIS. They will then be invited to attend for a study visit during which eligibility will be assessed and consent will be obtained.

There will be no randomisation since the measurement protocol will be the same for all participants. The measurement itself aims to reduce bias during muscle measurements.

Screening and Eligibility Assessment

Screening and eligibility will be assessed during the preliminary conversation with the potential participants when they express interest in the study. The CI will also ensure the participant is aware of the preparation needed to attend the visit (no exercise conducted in the hour before and to have an empty bladder on arrival). Eligibility will be assessed again at the study visit to ensure the participant is still eligible to take part.

Informed Consent

Only participants who fulfil the inclusion criteria will be able to consent. Participants who lack capacity will not be included in this study. Consent will be obtained by the CI at the study visit before any study activity begins.

Study visit

There is only one study visit for this study, so all study activities will occur on the same day at the Posture and Mobility Centre, Treforest or the Artificial Limb and Appliance Centre, Rookwood Hospital.

Eligibility for the study will be checked against the inclusion and exclusion criteria, including the requests to not have done heavy exercise for an hour before the measurements and also to have emptied their bladder before attending for the visit.

Any concerns will be also be addressed appropriately

Following the eligibility check, the CI will ensure the participant has read the PIS and fully understands it before obtaining informed consent.

Participants will be assigned a number in order to anonymise their data and only the main investigator will have access to this database of participants.

Additional information following the COVID-19 pandemic

In order to reduce the risk of coronavirus infection to the participants and to the investigators the participants will be contacted on the morning of the planned visit to assure them that the investigator is healthy and has no coronavirus symptoms and also to ask the participants to confirm that they are healthy and have no coronavirus symptoms. If the participant is unwell or the investigator is unwell the visit will not go ahead and will be rescheduled if the participant still wishes to still participate.

All of the equipment and surfaces in the room for the visit will have been cleaned prior to the study visit. They will all be cleaned again after the visit.

At the visit the participant will be asked to wash their hands and to wear a disposable mask that they will be given. The investigator will also wash their hands, wear gloves, a disposable apron and a disposable mask. Social distancing according to current guidelines will be maintained as far as reasonably possible although close contact will be necessary for the measurements.

Following the visit, the CI will dispose of the participant's mask and advise them to wash their hands again.

The following data will then be collected by the CI and written in a Case Report Form (CRF):

Gender

Date of birth (to ascertain age)

Height (to calculate BMI)

Weight (to calculate BMI)

Waist measurement (to calculate RFM index, considered an alternative indicator of health).

Medical history to ensure no existing neuromuscular, active arthritis or cardiac conditions or active implanted devices

Perceived level of fitness – using the NHS scale https://www.nhs.uk/live-well/healthy-weight/bmi-calculator/ (to gauge muscle ability)

A quantitative measurement method will be used in conjunction with a structured initial questionnaire relating to physical characteristics (e.g. height, weight, waist measurement, date of birth to indicate age and perceived level of fitness https://www.nhs.uk/live-well/healthy-weight/bmi-calculator/).

The CI will then attach electrodes to the arm of the participant and they will be asked to relax for 10 minutes.

The measurement device is an ImpediMed IMP SFB7 (CE 0129 marked) and is portable. EIM passes an imperceptible AC current (less than 1 mA) through the muscle under investigation and the impedance of that muscle is then recorded through a range of frequencies or at chosen frequencies.

Measurements of EIM of the relaxed muscles will be recorded in the CRF followed by measurements of EIM in the contracted muscle.

Electrodes will be carefully removed from the participant and they are invited to relax for a further 5 minutes and have a drink of water.

The participant's involvement in the study will end after the measurements have been taken.

Sources of error will include placement of electrodes. These will be placed as far as possible in line with SENIAM (Surface ElectroMyography for the non-invasive Assessment of Muscles) guidelines. Error may also occur due to inconsistent contraction of the muscle under observation. Inconsistent height, weight and waist size measurements. The same instruments for these measurements will be used.

Discontinuation/Withdrawal of Participants from Study

The data from any participants who withdraw or who are discontinued from the study will have their data retained up to that point. Reason for withdrawal or discontinuation will be recorded.

Study Amendments

It is the sponsor's responsibility to classify amendments as being non substantial or substantial. The CI will seek advice from C&VUHB R&D office prior to submission to the relevant bodies. The CI will seek approval for any substantial amendments to the protocol or other study documents from Health and Care Research Wales (HCRW) and Research Ethics Committee (REC). The NHS R&D Office(s) will need to confirm capacity and capability prior to implementation. Amendments to the protocol or other study documents will not be implemented prior to these approvals being granted. Non substantial amendments should be notified to the REC for information.

Definition of End of Study

The study will end after the last participant visit. There are no follow ups.

PRODUCTS, DEVICES, TECHNIQUES AND TOOLS

Devices: The device used for the EIM measurements is an ImpediMed IMP^{TM} SFB7 multifrequency body impedance meter. It is CE marked as a medical device, it is classified as electrical classification type BF, it meets the requirements of IEC 60601-1-2 (electromagnetic compatibility) and is manufactured in Australia.

The device records the electrical impedance between two pairs of electrodes attached to the arm of the volunteer. The electrodes are supplied by the manufacturer. Only single use electrodes supplied by the manufacturer will be used.

Only the CI will be using the device to make measurements. Training has been provided by the manufacturer.

Further demographic data will be collected using calibrated scales and a height measurement device.

SAFETY REPORTING

It is not anticipated that there will be adverse or serious adverse events associated with this study. However, in the event that they do occur they will be managed in accordance with Cardiff and Vale UHB standard operating procedures (SOPs) as appropriate. Only adverse or serious adverse events associated with the study will be recorded.

Urgent Safety Measures and Serious Breaches of GCP

The CI may take immediate safety measures to protect research participants against any hazard to their health or safety without prior authorisation from the REC or sponsor. However, they must alert the sponsor as soon as possible of any such urgent measures by contacting the Cardiff and Vale UHB R&D Office and CI. The CI will notify the REC of the presenting issue within 3 days of the urgent measure setting out the reasons for the urgent measure and the plan for further action. If a site PI identifies the presenting issue, he or she should also inform their local R&D department.

In the event that a serious breach of GCP is suspected, this will be reported to the sponsor and REC immediately and will be investigated by the sponsor. Any corrective action required will be undertaken by the CI and REC informed. If necessary a protocol amendment will be submitted for review.

STATISTICS AND ANALYSIS

Description of Statistical Methods

The two hypotheses being tested in this study are:

The EIM measurement of passive and active muscle is not significantly different.

EIM measurements in younger and older adult volunteers is significantly different.

Measurements of EIM on passive and contracted muscle will be compared using t-test statistics to test the first hypothesis with an expected P value of $P< 0.05$ would indicate that this is correct. That is, EIM measurement of active and passive muscle will coincide or be a very similar value 95% of the time, there is a 5% chance that it is a random error. If this is the case then the results are significant.

An analysis of the EIM measurement variation with age will be tested with a t-test to identify if there is a significant change with age. An expected P value of $P<0.05$ that this is correct. That is, the EIM measurement of younger people will differ 95% of the time from that of older people. It is proposed to use age groups 18-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90, 91-100.

The Number of Participants

20 Participants are planned, to be recruited over a six month period. The sample should be an age cross-section of healthy volunteers through a poster campaign. Given that the population of healthy volunteers is very large, this research study is a pilot sample. Similar studies comparing EIM measurements and age have used far

smaller samples (Vilaca et al., 2014; Rutkove et al., 2017) but have concentrated on specific patients or age groups.

Analysis of Outcome Measures/Endpoints

The primary aim of this research is to test whether EIM is an objective measure of muscle ability, this is carried out by measuring EIM in arm muscles in healthy participants when they relax and contract the muscle.

The endpoint will be after the last participant visit.

DATA MANAGEMENT

Access to Data

Direct access will be granted to authorised representatives from the sponsor and host institution for monitoring and/or audit of the study to ensure compliance with the relevant data protection legislation.

Data Recording and Record Keeping

A paper CRF will be used to collect data. The CRFs will be kept in a folder in a locked filing cabinet. A database will be designed to record the demographics and the EIM data from the paper CRF.

Data will be collated using SPSS, which is available for students registered at Manchester University or Liverpool University.

Participants will be allocated an anonymised participant ID number in numerical reference in sequential order. The numerical reference will allow anonymisation of the data in the database. A table linking the participant's name to the numerical reference will be kept secure in a separate document which will be password protected and backed up on the C&VUHB server network to enable data privacy. The data will not be transferred.

All data will be stored on C&VUHB encrypted PCs/servers in order to comply with data security and backup.

The CI is responsible for the data entry, quality of the data and data analysis. The CI will be data controller and data processor.

Participant Confidentiality and Data Protection

All investigators and study site staff must comply with the requirements of the General Data Protection Regulation (GDPR) and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

This study will comply with the GDPR and Data Protection (2018). Which require data to be de-identified as soon as it is possible to do so. The study staff will ensure that participants' anonymity is maintained and that participants will only be identified by a participant ID number on all study documents and any electronic database, with the exception of the participant details needed to facilitate sharing of an executive summary of the study results. All documents will be stored securely and only be accessible by study staff and authorised personnel.

As described above, all data will be recorded on C&VUHB encrypted PCs. The CRFs will be kept in a folder in a locked drawer as described above. All electronic data will be stored in password protected areas where there is C&VUHB backup of the data.

All participants will be allocated a sequential number to anonymise them in the database of information. A separate password protected, backed up document recording the link will be stored outside of the database.

The CI will be the data custodian

Data will be stored in accordance with the C&VUHB policies for retention.

13.4 Record Storage and Retention

The TMF and ISF containing essential documents will be kept for 5 years after completion of study. Documents (paper and electronic) will be retained in a secure location during and after the study has finished. Essential documents generated at the site for the agreed archiving period in accordance with the C&VUHB's SOPs.

Essential documents pertaining to the study shall not be destroyed without permission from the sponsor.

QUALITY ASSURANCE PROCEDURES

The study may be subject to inspection and audit by C&VUHB R&D office under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research 2017.

ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in compliance with the principles of the Declaration of Helsinki (2013) and the principles of GCP and in accordance with all applicable regulatory guidance, including but not limited to the UK Policy Framework for Health and Social Care 2017.

This protocol and related documents (and any subsequent amendments) will be submitted for review to the relevant parties (HCRW and REC).

Annual progress reports and a final report at the conclusion of the study will be submitted to the REC within the timelines defined.

Review and Approvals

Ethical Approval and HRA/HCRW approval

Before the start of the study, approval will be sought from HCRW and REC for the protocol, informed consent forms and other relevant documents e.g. advertisements.

Amendments that require review by HCRW and REC will not be implemented until approval is granted. The CI (or delegate) should submit any amendments to their National Coordinating Unit, (HCRW). The HCRW Permissions Service will assess and approve the amendment.

The CI (or delegate) also needs to notify the R&D offices and local research teams the amendment(s). The R&D Office(s) will have 35 days from receipt of the amendment to confirm capacity and capability.

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File

A progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the CI's responsibility to produce the annual reports as required.

The CI will notify the REC of the end of the study.

If the study is ended prematurely, the CI will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the REC.

Peer Review

The literature review for this study has been reviewed by Professor Colin Gibson and Professor Tony Fisher. A science review of the study facing documents has also been reviewed by them.

Potential healthy volunteers have been asked for their comments and response to the volunteer recruitment poster, the study information sheet and the consent form.

Governance Review

The study will be assessed for governance and legal compliance by HCRW. Once all checks are satisfied HCRW will issue HRA/HCRW approval. The study should not commence at any site until local confirmation of capacity and capability is also received via email by the CI.

Reporting

The CI shall submit once a year throughout the study or on request, a progress report to the REC and sponsor. In addition, an end of study notification and final report will be submitted to the same parties.

Expenses and Benefits

No expenses are payable for volunteers.

INDEMNITY AND FINANCE

Indemnity

This is an NHS-sponsored research study, and the NHS indemnity scheme therefore applies. If there is negligent harm during the study when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. The NHS indemnity scheme does not cover non-negligent harm.

Financial and other competing interests

There are no financial or other competing interests

PUBLICATION AND REGISTRATION POLICY

Ownership of the data arising from this study resides with the study team and their respective employers. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared. Authors will acknowledge that the study was funded as part of the National School of Healthcare Science (NSHCS) HSST Programme which requires the completion of a DClinSci and other contributors will be acknowledged.

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

REFERENCES

Please see attached list of references used in the literature review. – see References section

A4.4 Participant Information Sheet

PARTICIPANT INFORMATION SHEET V2.1

Study Title: An investigation into an objective measure of muscle quality, function and ability.

Chief Investigator (CI): Dr Stephanie Wentworth

You are being invited to take part in a study with Rehabilitation Engineering Unit (REU), a department within Cardiff and Vale University Health board (C&VUHB). Before you decide, it is important for you to understand why the research is being done and what it will involve.

Please take time to read the following information carefully and discuss it with others if you wish. The CI will go through the information sheet with you. Please ask the CI if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to participate.

What is the purpose of this study?

The aim of the study is to test whether a measurement of muscle ability and function can be done more objectively; that is, whether it can be done without the person being tested influencing it consciously or unconsciously. The measurement carried out on healthy volunteers of all ages, can help us to understand if this is possible and will help us understand more about the quality of the muscles and their ability. It then has the potential to be used with patients who have muscle diseases.

Why have I been asked to take part?

We are inviting volunteers to take part aged 18 and upwards,

who don’t have an existing neuromuscular disorder, cardiac disease or active implanted device like a pacemaker, active arthritis or are pregnant.

How can I take part?

You may have become aware of this study from someone you know or you may have responded to the call for volunteers poster and emailed the CI. In response to your interest the CI has given you this information sheet and will explain the study to you and answer any questions you might have. You will be asked whether or not you want to take part. If you would like to, you will be asked to sign a consent form and then we can begin the study.

Do I have to take part?

It is up to you to whether or not to take part. If you do decide to take part you will be given this information sheet to keep and a copy of your signed consent form. If you decide to take part, you are still free to withdraw at any time without giving a reason. Should you decide not to take part, you do not have to provide a reason for this choice.

What will happen to me if I take part?

If you wish to take part in this study you will be assessed in the Posture and Mobility Centre (PMC) in Treforest or the Artificial Limb and Appliance Centre (ALAC) at Rookwood Hospital; all participants will be sent a map and directions to the appropriate location. You will be asked to attend the PMC or ALAC where you will be screened for eligibility and after you have signed a consent form, if you decide you would like to take part, a clinical assessment will be carried out. The session may last up 30 minutes.

What will I have to do?

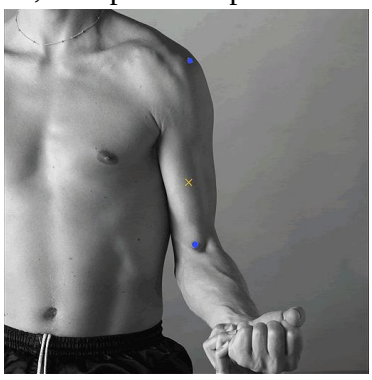
If you agree to take part you, the CI will contact you and ensure that before attending the assessment visit, you do not exercise intensively or drink anything for an hour beforehand and empty your bladder shortly before the visit. Excessive exercise (e.g. running or doing exercises in the gym) and drinking close to the time measurements are taken may affect the results.

During the initial contact with the CI, you will be checked for your eligibility and once again at the visit in case anything has changed and you will be asked to sign an informed consent form. You must be 18 years old or older. You cannot take part if you have any neuromuscular or cardiac condition including any active implanted device, active arthritis or are pregnant.

Additional information following the COVID-19 pandemic
In order to reduce the risk of coronavirus infection to you and to the investigators you will be contacted on the morning of your planned visit to assure you that the investigator is healthy and has no coronavirus symptoms and also to ask you to confirm that you are healthy and have no coronavirus symptoms. If you are unwell or the investigator is unwell the visit will not go ahead and will be rescheduled if you still wish to participate.

All of the equipment and surfaces in the room for the visit will have been cleaned prior to your visit. They will all be cleaned again after your visit.

At your visit you will be asked to wash your hands and to wear a disposable mask that you will be given. The investigator will also wash their hands, wear gloves, a disposable apron and a disposable mask. Social distancing according to current guidelines will be maintained as far as reasonably possible although close contact will be necessary for the measurements.



Following the visit, we will dispose of your mask and advise you to wash your hands again.

There will then be a short assessment to measure your height, weight and waist size in order to classify your Body Mass Index (BMI) and your Relative Fat Mass (RFM) index which are used as a measure of your health.

In the clinical examination the CI will examine the bones, muscles and joints of your arms. This is normally done with you sitting relaxed in a chair. The CI may need to feel different points on your bones and muscles and may mark these points with dots of marker pen or eye liner. The CI may also measure your arm.

Two double electrode sensors will be attached to your skin around the muscle that will be measured. The sensors are designed to produce a very small (less than 0.5mA) current which is passed through your muscle and the resistance to the current is detected using the second pair of electrodes. The current is less than it is possible to feel, so you should experience no sensation from the measurements. Before attaching the Electrical Impedance Myography (EIM) sensors, the CI will need to prepare the skin, using a special gel. The CI may also need to remove small patches of hair where the sensors are going to go. The sensors themselves are small and flat. These will be attached to your skin using adhesive which is part of the electrode.

Example picture from Seniam (surface electromyography for the non-invasive

Prior to the start of the measurement you will be asked to sit quietly and relax for 10 minutes, this is important for helping to ensure that your muscles are in a relaxed state and that you feel comfortable and mentally relaxed. This process will be carried out with the utmost professionalism and a sign is placed on the door telling other staff not to enter whilst the assessment is in progress.

You will be asked to remain relaxed while the first set of measurements is carried out.

You will then be asked to stay still and relaxed for a further 5 minutes.

For the second set of measurements you will be asked to contract the muscles under assessment.

You will be free to stop for a break at any time although if you need to eat or drink anything during the assessments the measurements will not be valid for the study.

Following the assessment you will be asked to wait a further 5 minutes and have a drink to ensure that you have experienced no effects from the measurements. None are expected.

Are there any risks in taking part in this trial?

The sensors are placed with hypoallergenic (to prevent allergies) medical grade sticky adhesive which may cause some mild discomfort when it is being removed similar to removing a small sticking plaster. Sometimes we also need to shave very small patches of skin where sensors are going to be placed.

The EIM measurement involves passing a very small electrical current through the muscles on your arm; this current is so small that it is very unlikely that you will feel anything at all. The electrical current perception level is approximately 0.5mA and the EIM measurement is 0.2mA. However, there is a very low risk of feeling a slight tingling sensation if anything at all.

Are there any benefits in taking part in this trial?

There is no intended clinical benefit to the participant from taking part in the study. The information the study team get from this study may help us to provide future patients with movement problems with improved treatment options. There are no payments for taking part in the study.

What will happen if I do not want to carry on with the study?

You are free to withdraw from the study at any time and do not have to give a reason. If you withdraw from the study, we will retain your data collected up until this point.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be

kept strictly confidential. Your data will be anonymised and will be stored on a secure server at C&VUHB on a password protected computer and only the research team will be able to access it. Identifiable information (e.g. contact details) will not be shared outside the research team and will be kept separate to the study data. Your personal information and results from the study will be stored on secure computers within the Cardiff REU, C&VUHB and only accessed by the CI involved in the study. Should you wish to withdraw from the study, you are free to do so but data collected will be retained. At the end of the study your data will be archived for 5 years in accordance with good research practice and C&VUHB data protection regulations and archiving procedure.

What will happen to the data collected in the study?

Data will be kept secure for 5 years in line with good research practice and data protection regulations imposed by C&VUHB in line with the General Data Protection Regulations 2018. All data obtained during the study will be kept confidential. Access to data will only be available to the investigators attached to the project and the REU, C&VUHB.

C&VUHB is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. C&VUHB will keep identifiable information about you for up to 5 years after the study has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable

information possible. You can find out more about how we use your information by contacting cav.ig.dept@wales.nhs.uk.

How will we use information about you?

We will need to use information from you for this research project.

This information will include your initials, name, contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data for 5 years so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team

- by sending an email to cav.ig.dept@nhs.uk

Who is organising and funding the study?

Clinical Scientists/Engineers at the REU, C&VUHB are carrying out the study. The study is not funded by commercial sources. This study forms part of the NSHCS Higher Specialist Scientist Training (HSST) programme. This programme requires the completion of a DClinSci; jointly supported through the University of Manchester, the University of Liverpool and C&VUHB as the employing health organisation.

Who has reviewed the study?

Before any research goes ahead it has to be checked by a research ethics committee (REC) to make sure that the research is safe to conduct. This study has been reviewed and approved by REC.

What if there is a problem?

This study is being led by Dr Stephanie Wentworth at C&VUHB. If you have any problems about this study, our contact details are at the end of the information sheet. If you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal C&VUHB complaints mechanisms should be available to you. Please discuss any complaints about the way our study has been carried out with us first. If you are still unhappy and want to formally complain, please contact concerns@wales.nhs.uk.

Thank you for reading this information sheet.

If you would like to take part in this study, then contact Stephanie Wentworth (Senior Clinical Engineer) who will arrange a convenient time and date for you to attend using the contact details below;

Dr Stephanie Wentworth (Senior Clinical Engineer)

Rehabilitation Engineering Unit

ALAS Posture and Mobility Centre

Unit A, Bridge Road, Treforest Industrial Estate

Cardiff and Vale University Health Board

CF37 5TF

Telephone: 02920 313931

Email: stephanie.wentworth@wales.nhs.uk

A4.5 Informed Consent Form

INFORMED CONSENT FORM V1

Study Title: An investigation into an objective measure of muscle quality, function and ability.

Chief Investigator: Dr Stephanie Wentworth

Participant ID: …..…….. Initials: …… Date of Birth: ……...

You DO NOT have to sign this document. Please DO NOT sign this document unless you fully understand it. If there is ANYTHING which you do not understand please do not hesitate to ask for a full explanation.

To confirm agreement with each of the statements below, please initial each box and delete where applicable:

1. I confirm that I have read and understand the information sheet dated _____ for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that even if I withdraw from the above study, the data collected from me will be used in analysing the results of the study. ☐

3. I understand that any information that could identify me will be kept strictly confidential on a secure password protected computer and that no personal information will be included in the study report or other publication. ☐

4. I agree to take part in the above study.

_____ _____

Name of the participant Participant's signature and the date the participant signed the consent form

_____ _____

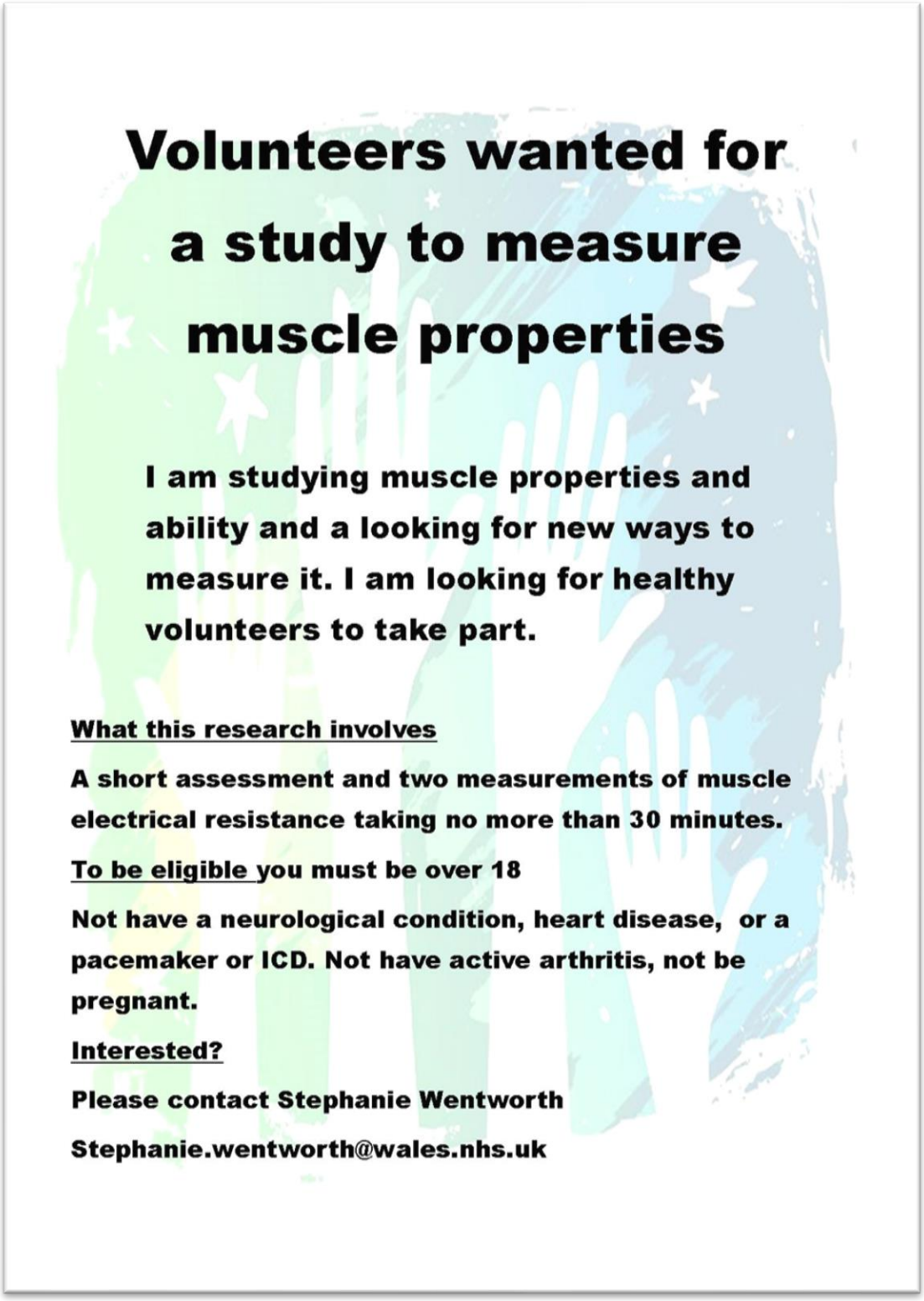
Name of the researcher Researcher's signature and the date the researcher signed the consent form

_____ _____

Name of the person taking consent If different from researcher	Individual’s signature and the date the individual signed the consent form

Original to be retained in the site file. 1 copy for the patient.

A4.6 Volunteer poster



A4.7 Data collection sheet

An investigation into an objective measure of muscle quality, function and ability.

Data collection sheet

Participant number

Eligibility assessment

Condition	Yes/No	Eligible
Volunteer		Y
Over 18		Y
pre-existing neuromuscular disease		N
ICD/ pacemaker/ heart disease		N
Other implanted electrical device		N
active arthritis		N
Pregnant		N
Well today		Y
Able to give informed consent		Y

Eligible =

Consent =

Age		
Weight		
Height		
Waist measurement		
BMI		
RFM		

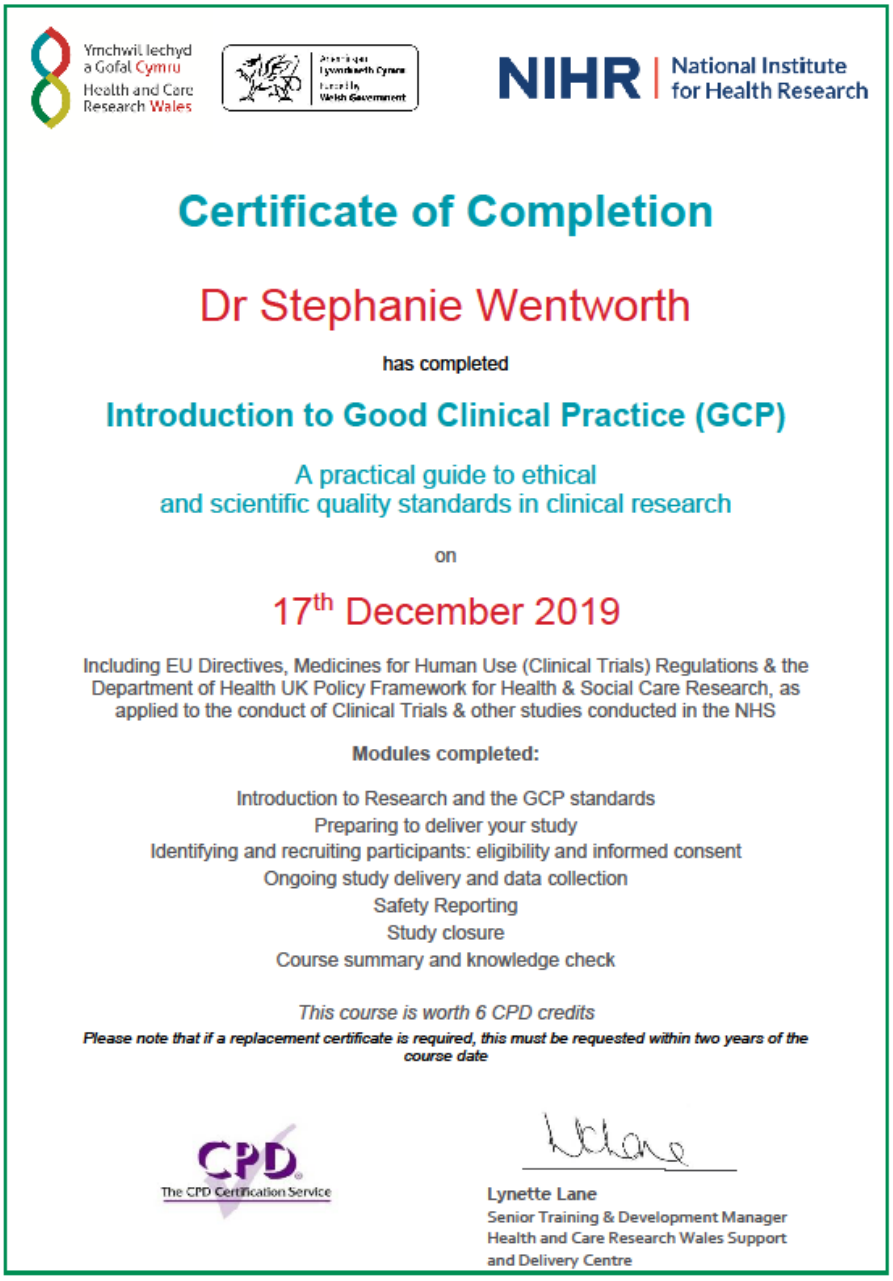
EIM measurements

File name	Condition	Done
	Relaxed	
	Activated	
	Relaxed	
	Activated	

SCHEDULE OF STUDY PROCEDURES

Procedures	Visit 1
Eligibility assessment through screening	X
Medical history	X
Informed consent	X
Demographics (age, height, weight, waist size)	X
Physical examination for placement of electrodes	X
Assessment 1 Relaxed EIM	X
Assessment 2 Muscle contracted EIM	X
Adverse event assessments	X

A4.8 Good Clinical Practice Certificate evidence



Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Llywodraeth Cymru
Welsh Government

NIHR | National Institute for Health Research

Certificate of Completion

Dr Stephanie Wentworth

has completed

Introduction to Good Clinical Practice (GCP)

A practical guide to ethical
and scientific quality standards in clinical research

on

17th December 2019

Including EU Directives, Medicines for Human Use (Clinical Trials) Regulations & the Department of Health UK Policy Framework for Health & Social Care Research, as applied to the conduct of Clinical Trials & other studies conducted in the NHS

Modules completed:

Introduction to Research and the GCP standards
Preparing to deliver your study
Identifying and recruiting participants: eligibility and informed consent
Ongoing study delivery and data collection
Safety Reporting
Study closure
Course summary and knowledge check

This course is worth 6 CPD credits

Please note that if a replacement certificate is required, this must be requested within two years of the course date

CPD
The CPD Certification Service

Lynette Lane
Senior Training & Development Manager
Health and Care Research Wales Support and Delivery Centre

Appendix 5 Innovation Proposal: Mobile arm support service

A5.1 Description

Weakness of arm muscles can have a devastating effect on patients' feelings of self-worth and independence. The ability to reach for and interact with the environment is a need from earliest life. Assistance with eating, drinking, personal care and interests is often an overlooked cost; it may be met by unpaid support from family and friends or funded care assistance may be required. Enabling a patient to carry out some of those tasks independently not only supports their mental health but frees up the time for family and friends to interact in a more appropriate way for their relationship and also for carers to carry out other support tasks for the patient that they would otherwise not have time to do. The high cost to society of the loss of independence of one person is often hidden partly because it falls between health and social care and also because it can be difficult to quantify.

Mobile arm supports (MAS) are assistive devices designed to support people with weak arm muscles who cannot lift their arms to carry out everyday activities of daily living such as eating and personal care. They can be simple mechanical devices, more complex mechanical devices with assistive lifting or electrically powered devices. Conditions in which people develop arm weakness include motor neurone disease (MND), multiple sclerosis (MS), muscular dystrophy (MD), stroke, and other neurological conditions.

Development of a mobile arm support service would assist not only the patients with arm weakness but their support network, their healthcare and social care workers. It may also improve their mental health as they gain renewed independence. The impact on society of a simple solution is an important consideration. Alongside other

assistive technology devices the development of a mobile arm support lies optimally with those trained in medical device application, development and management. The simple mechanical device can be modified to meet individual patient requirements by those trained to do this safely.

An 18-month mobile arm support pilot was launched by Cardiff and Vale University Health Board (C&VUHB) Rehabilitation Engineering Unit in 2017 (Wentworth and Dube, 2018). It was resourced from local research funding and followed a request from a neurology consultant. No mobile arm support service was available in Wales because it was possibly perceived as a cost rather than adding value. Experience of supporting MND patients in the Oxford Motor Neurone Disease Care and Research Centre (Oxford MND Centre - Oxford University Hospitals (ouh.nhs.uk)), informed the start-up and engaging with experienced colleagues in Oxford and Birmingham enabled a small support network to be set up.

The pilot project, led by a Senior Clinical Engineer and a Trainee Rehabilitation Engineer, focussed on MND patients and received referrals from Occupational Therapists (OTs) and Physiotherapists.

A5.2 Value

Value in healthcare can be expressed using the equation from the Health Financial Management Association (HFMA, 2015) and also as applied to medical devices by Hegarty et al., (2017). The equation below is adapted from these sources.

$$Value = \frac{Benefit\ (Health\ outcomes)}{Cost\ (of\ delivering\ the\ outcomes)}$$

National Institute for Health and Care Excellence (NICE) (2013) define how they measure cost effectiveness linking it to ‘quality-adjusted life years’ (QALYs) and in the 2013 document interventions costing the NHS less than £20,000 per QALY were

considered cost effective. Taylor (2014) describes healthcare as ‘messy’ in that patients (as people) do not draw distinctions between outcome and experience. A healthcare episode of care may be successful from a procedural aspect but if the experience is difficult, traumatic or perhaps the patient does not feel valued and supported then their experience may be negative. The ‘Value’ equation can be expanded using Taylor’s perspective by considering ‘Benefit’. Who receives the benefit? The benefit can be to all of the stakeholders not just the patients.

$$Value = \frac{Clinical/health\ outcome\ x\ (patient\ experience\ and\ other\ stakeholders\ experience)}{Costs\ (of\ delivering\ the\ outcomes)}$$

Adapted from Goodall, (2015), Welsh Government (2019).

The value will depend on the needs and expectations of the stakeholders who will include the patient and the carers (both formal and informal), as well as the healthcare professionals. They will experience different benefits of the service. Patient-focussed care puts the patient at the centre and the patient is best placed to decide the benefit and the value. The benefit will include the time and well-being of all the stakeholders. The cost is the cost of the resources, the device and the staff needed to manage and support it. The concept of wider benefit can also be considered in the light of ‘social return on investment’ (SROI), (Arnold, 2018 and the example in Public Health England, 2016; DH, 2010; Hurst et al., 2019). This value equation can help to assess and evaluate qualitatively the development of a mobile arm support service. The table below focusses on clinical outcomes, patient experience and costs.

Table A5.1 Value, benefits and costs of a mobile arm support service

Without mobile arm support				**With mobile arm support (Approximate cost per patient of service = £1,300)[1]**			
Value	Clinical outcome	Patient/ other stakeholder experience	Cost	Value	Clinical Outcome	Patient/ other stakeholder experience	Cost
No added value	**(Patient)** Continues to rely on carers for: feeding, grooming, reaching objects	**(Patient)** Lack of independence, increased helplessness, Decreased choice Decreased dignity Increased anxiety **(Family/ friends/ unpaid carers)** Anxiety Stress Time needed for caring Loss of dignity **(Paid carers/ support workers)** Time spent on feeding and immediate support tasks Time spent on stretching/exercise tasks Time spent on feeding tasks	Negative and difficult to calculate as very subjective. Consider QALYs (NICE, 2022 and SROI, 2018) Negative Mental health impact. Consider SROI (2018) No change in cost but more tasks to be performed in funded time. Estimate £20/hour, 3 hours/day for feeding & basic support. = £420 / week =£1,680 / month =£21,900 /year	Added value for patients, family, unpaid carers and healthcare staff	**(Patient)** Increased independence Ability to feed Ability to touch/scratch e.g. nose Ability to reach near objects	Increased independence Ability to feed themselves Ability to scratch/touch e.g. nose Ability to reach near objects Ability to operate computer keyboard. Increased dignity Increased choice Decreased dependence on others Decreased anxiety Improved mental health Improved mood **(Family/ friends/ unpaid carers)** Increased happiness for patient Increased quality family time **(Paid carers/ support workers)** Increased time for tasks other than feeding and immediate supporting tasks	Positive and difficult to calculate as very subjective. Consider QALYs (NICE, 2022) and SROI (2018) Positive mental health impact. Consider SROI (2018) Positive impact, paid carer time not spent on feeding and basics. Support can be spent on other important tasks, e.g. personal care, cooking and cleaning.
Totals			**£1,680/month**				**£1,300**

[1] See Table A5.2 and A5.3 for mobile arm support service cost details

Table A5.1 Device and staffing costs for mobile arm support (MAS) service

Resource	Cost (2017)
Jaeco table-mounted large mobile arm support	£267
Cover for forearm support	£30
Staffing time 1 x Clinical Engineer/Scientist 1 x Rehabilitation engineer	£80 per member of staff per hour

Table A5.2 Estimated cost for service

Assessment of patient in their own home by Clinical Engineer and Rehabilitation Engineer (includes transport) – 2 hours	£320
Issue of 2 x Jaeco MAS with covers	£594
Review after 2 weeks by Clinical Engineer or Rehabilitation Engineer (includes transport) 1 hour	£80
Bespoke parts to support hand, attach stylus etc – 4 hours design and manufacture time (includes transport and fitting) – Rehabilitation Engineer	£320
Approx. total cost	£1,314

A5.3 Business case

A clear benefit is demonstrated in the above example. Assessment and issue of a mobile arm support (MAS), including design and manufacture of bespoke parts, costs approximately £1,300. Carer feeding costs (**the only calculable cost**) for 1 month = £1,680. Saving/benefit = £380.

Actual savings and benefits will be much higher because of the difficulty in putting a monetary value on independence and quality family time. These could be estimated using QALYs but would include more than patient QALYs. The benefits to society can be estimated from SROI calculations.

Aims: To provide a mobile arm support service to users with arm weakness

Patient groups identified: MND, MS, MD, Stroke. Support for activities of daily living and maintenance of arm flexibility.

Benefits: Improved mental health for patients and their families and carers, improved independence for patients and reduction in reliance on carer and

healthcare support. Support of patients in the community – reduction in hospital admissions.

The availability of bespoke patient-centred designs for improving use of the mobile arm support.

Resources: Rehabilitation Engineering Unit resources: Clinical Engineer and Rehabilitation Engineer to provide assessment, set up and review, develop bespoke parts under the regulations and to run the library service of MAS devices.

Device library, facilities for storage, decontamination and disposal of devices.

Financial costs: Staffing, transport, devices and parts, access to design and workshop facilities for the design and fabrication of bespoke parts.

A5.4 Relation to the DClinSci project

Part of the patient assessment for a MAS is evaluating their arm strength and ability, usually carried out at the patient's home. The most widely used assessment is the manual muscle test; this is dependent on the skill and strength of the assessor. A more objective way to assess the patient would better inform the clinical appropriateness of trialling and issuing a mobile arm support and provide value to the service.

A5.5 Stakeholder engagement

The pilot was developed using learned and shared experience from colleagues in Oxford and Birmingham. MND patients were referred to the service by OTs and Physiotherapists linking with the Motor Neurone Disease Association (MNDA) co-ordinators. The pilot service was supported by research funding and MNDA

endowment funding. Patient opinion and comments were actively sought and local therapists also provided feedback.

Providing a patient with a device to help them eat unaided, scratch their nose or operate a keyboard were all expressed aims.

A5.6 Executive/Lay summary

Provision of a device to support arm weakness in patients with conditions such as MND and MS has been shown to improve their independence and feeling of well-being. Timely response from referral to issue is crucial for such a service; response must be fast for MND patients to benefit. For other patients, using a mobile arm support has helped them to maintain their arm flexibility and has the potential to be supportive in rehabilitation following stroke.

Provision of mobile arm supports is available in England with centres in Oxford and Birmingham. For equity the development of a mobile arm support service in Wales is needed. It is not currently funded as it is possibly perceived as a cost rather than understanding the added value and benefit to all of the stakeholders.

A pilot mobile arm support service demonstrated the benefit of the device for MND patients but accessing resource to establish a sustainable service has been difficult. NHS funding has not been achieved despite the evidence of improved independence, reduction in carer requirements and improvement in mental health. While appearing to be a simple solution, clinical engineers are well-placed to assess patients and provide the mobile arm supports and design and develop bespoke parts for focussed patient care. The ongoing effects of mobile arm supports have far reaching consequences for patients in the community and their families, carers and society as a whole.

Appendix 6 CH3 A and B Units

DClinSci Appendix – List of AMBS A units and Clinical Biomedical Engineering B units together with assignments – Stephanie Wentworth

AMBS – A Units		
Unit title	**Credits**	**Assignment wordcount**
A1: Professionalism and professional development in the healthcare environment	30	A1 – assignment 1 – 2500 words Group work/presentation – 10 minutes (10%) A1 – assignment 2 – 3000 words
A2: Theoretical foundations of leadership	20	A2 – assignment 1 – 3000 words A2 – assignment 2 – 3000 words
A3: Personal and professional development to enhance performance	30	A3 – assignment 1 – 1500 words A3 – assignment 2 – 4000 words
A4: Leadership and quality improvement in the clinical and scientific environment	20	A4 – assignment 1 – 3000 words A4 – assignment 2 – 3000 words
A5: Research and innovation in health and social care	20	A5 – Group work/presentation – 15 minutes (25%) A5 – assignment – 4000 words
Clinical Biomedical Engineering – B Units		
B1: Clinical Practice for Clinical Biomedical Engineers	10	3000 word assignment
B2: Systems Engineering	10	3000 word assignment
B3: Clinical Computing	10	Group presentation 1500 word assignment
B4i: Health Economics	10	3000 word assignment
B4ii: Health Technology Assessment	10	3000 word assignment
B6: Modelling and Simulation	20	2 x 3000 word assignments
B8/9: Specialist CBE Skills and Practice	20	3000 word assignment
B10: Leading CBE Services	20	In pairs trainees to organise an event 1000 word reflection on event
Generic B Units		
B5: Contemporary issues in healthcare science	20	1500 word assignment + creative project
B7: Teaching Learning Assessment	20	20 minute group presentation