Clinical Trial Protocol

Trial Title: **PO**sterior **L**aminectomy and **FIX**ation for **D**egenerative **C**ervical **M**yelopathy **[POLYFIX-DCM]**

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Chief Investigator: Dr Mark Kotter

Principle Investigator, NIHR Clinician Scientist, Honorary Consultant in Neurosurgery

University of Cambridge, Neurosurgery Unit & Stem Cells, Department of Clinical Neurosciences, Box167, Cambridge Biomedical Campus, Cambridge, CB2 0QQ, United Kingdom

Telephone: +447887790773

Email: mrk25@cam.ac.uk

Trial Sponsor: Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge

SAE Reporting: Cambridge Clinical Trials Unit (CCTU)

Email:

1 Protocol Signatures:

I give my approval for the attached protocol entitled POLYFIX DCM dated.....

Chief Investigator

Name: Mark R. N. Kotter

Signature: _____

Date: _____

Site Signatures

I have read the attached protocol entitled “POLYFIX DCM” dated ..... and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and 2005/28/EC, the Sponsor’s SOPs, and other regulatory requirements as amended.

In case of international trials with sites outside the EU the statement above may need to be amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

Principal Investigator

Name:

Signature: _____

Date: _____

2 Trial Management Committee(s) and Protocol Contributors

Chief Investigator	Dr Mark Kotter	Honorary Consultant in Neurosurgery Dept. of Clinical Neurosciences, Level 5, A Block, Addenbrooke's Hospital, Cambridge Biomedical Campus, Cambridge, CB2 0QQ Telephone: +44 1223 596029 Email: mrk25@cam.ac.uk
Trainee Chief Investigator	Mr Benjamin Davies	Specialist Trainee in Neurosurgery Cambridge University Hospital, Department of Neurosurgery, Hills Road, Cambridge, CB2 0QQ Telephone:01223 245151 Email: bd375@cam.ac.uk
Trial Statistician	Dr Simon Bond	Senior Statistician Cambridge Clinical Trials Unit (CCTU), Coton House, Level 6, Box 401, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ Telephone: + 44 (0)1223 596475 Email: simon.bond@addenbrookes.nhs.uk
Health Economist	Prof. Garry Barton	Health Economics Group, Norwich Medical S Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, Norfolk, NR4 7TJ Tel: 01603 591936 e-mail: g.barton@uea.ac.uk
Health Economist	Dr. David Turner	Health Economics Group, Norwich Medical S Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, Norfolk, NR4 7TJ
Neurosurgical Trial Management	Carole Turner	Dept. of Clinical Neurosciences, Level 5, A Block, Addenbrooke's Hospital, Cambridge Biomedical Campus, Cambridge, CB2 0QQ Email: clt29@medschl.cam.ac.uk
Trial and Data Management	CCTU	Cambridge Clinical Trials Unit (CCTU), Coton House, Level 6, Box 401, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ Telephone: + 44 (0)1223 254684
Trainee Neurosurgical Representative	Mr Edward Goacher	Specialist Trainee in Neurosurgery Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF Telephone: 07854438101 Email: Edward.goacher1@nhs.net

London Regional Centres Representative	Mr Edward Dyson	Specialist Trainee in Neurosurgery Guy's and St Thomas' Foundation Trust London edwarddyson@nhs.net
Neurosurgical Trials Expertise	Dr Angelos Kolias	Academic Clinical Lecturer, Specialist Trainee in Neurosurgery Cambridge University Hospital, Department of Neurosurgery, Hills Road, Cambridge, CB2 0QQ Telephone:01223 245151 Email: ak721@cam.ac.uk
Principal Investigator	Mr Mike Hutton	University Hospital Plymouth
Principal Investigator	Mr Rikin Trivedi	Consultant Spinal Surgeon Cambridge University Hospital, Department of Neurosurgery, Hills Road, Cambridge, CB2 0QQ Telephone: 01223 245151 Email: rikin.trivedi@addenbrookes.nhs.uk
Principal Investigator	Mr Sentil Selvanathan	Consultant Neurosurgeon Leeds General Infirmary, Leeds, LS1 3EX, Email: senthil.selvanathan@nhs.net
Trainee Neurosurgical Representative	Mr Oliver Mowforth	Specialist Trainee in Neurosurgery Cambridge University Hospitals, Department of Neurosurgery, Hills Road, Cambridge, CB2 0QQ Telephone:01223 245151 Email: om283@cam.ac.uk
Service and Patient Representative	Mr Iwan Sadler	8 Cwrt Myrddin Pentre Doc Y Gogledd, Carmarthenshire, Sa152ll Telephone: 01554 228399 Email: iwansadler@hotmail.co.uk
Neurosurgery Expertise	Professor Peter Hutchinson	Honorary Consultant Neurosurgeon Cambridge University Hospital, Department of Neurosurgery, Hills Road, Cambridge, CB2 0QQ Telephone: +44 1223 596029 Email: p.hutchinson@addenbrookes.nhs.uk
Protocol Contributor		
Physiotherapy and Rehabilitation Expertise	Dr Sukhivindra Kalsi-Ryan	Affiliate Scientist, KITE Research Institute |UHN; Assistant Professor Department of Physical Therapy, University of Toronto Telephone: +1 (416) 597-3422 X 6340 Email: Sukhvinder.Kalsi-Ryan@uhn.ca
Emergency Medicine / Intensive Care	Dr Virginia Newcombe	Honorary Consultant, Intensive Care and Emergency Medicine,

/ Neurotraumatic Imaging		Cambridge University Hospital, University Department of Anaesthesia.
Spinal Surgery Expertise	Mr Jibin Francis	Consultant Neurosurgeon Cambridge University Hospital, Department of Neurosurgery, Hills Road, Cambridge, CB2 0QQ Telephone: 01223 256182 Email: jibin.francis@addenbrookes.nhs.uk
Primary Care	Dr James Milligan	
Principal Investigator	Mr Martin Wilby	Consultant Neurosurgeon Department of Neurosurgery, The Walton Centre for Neurology and Neurosurgery, NHS Trust, Liverpool, Lower Lane, Fazakerley Liverpool, L9, 7LJ Telephone: 0151 525 3611 Email: martin.wilby@thewaltoncentre.nhs.uk
Principal Investigator	Mr Erlick Pereira	Reader in Neurosurgery, St George's, University of London Consultant Neurosurgeon, St George's University Hospitals, London SW17 0QT Email: erlick.pereira2@nhs.net
Principal Investigator	Mr Palaniappan Lakshmanan	Consultant Spinal Surgeon South Tyneside and Sunderland Sunderland Royal Hospital Email: lakunns@gmail.com
Principal Investigator	Mr Guy Wynne Jones	Consultant Spinal Neurosurgeon Spinal Unit Department of Orthopaedics The Newcastle upon Tyne Hospitals NHS Foundation Trust, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP Tel:01912821789 Email: g.wynne-jones@nhs.net
Co-Principal Investigator	Mr Prokopis Panaretos	Consultant Neurosurgeon The Newcastle upon Tyne Hospitals NHS Foundation Trust, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP Tel: 01912821787 Email: prokopis.panaretos@nhs.net
Principal Investigator	Mr Marcel Ivanov	Consultant Neurosurgeon Department of Neurosurgery, Royal Hallamshire, Glossop Road, Sheffield, S10 2JF Email: marcel.ivanov1@nhs.net
Principal Investigator	Mr Pierluigi Vergara	Consultant Spine Neurosurgeon Spinal Unit – Dept of Orthopaedics Ipswich Hospital - East Suffolk and North Essex Foundation Trust, Heat Rd, IP45PD

		Tel: 01473704812 Email: Pierluigi.Vergara@meht.nhs.uk
Principal Investigator	Mr Anthony Bateman	Consultant Spinal Surgeon University Hospitals of Derby and Burton, Uttoxeter Road, Derby, DE22 3NE Email: antony.bateman@nhs.net
Principal Investigator	Mr Marcin Czyz	University Hospitals Birmingham NHS Foundation Trust Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston Birmingham, B15 2GW Ext: 15818 Email: Marcin.Czyz@uhb.nhs.uk
Principal Investigator	Mr Chris Derham	Consultant Neurosurgeon Leeds General Infirmary, Leeds, LS1 3EX, Email: c.derham@nhs.net
Principal Investigator	Mr Giles Critchley	Consultant Neurosurgeon and Lead Spinal Surgeon Honorary Clinical Reader - Brighton and Sussex Medical School South East Neurosurgery and South East Spinal Surgery. Brighton and Sussex University Hospitals NHS Trust Tel: 01444 441881 ext 5701 Email: giles.critchley@nhs.net
Principal Investigator	Mr Andreas Demetriades	Consultant Neurosurgeon Edinburgh
Principal Investigator	Mr Ranna Dhillon	
Principal Investigator	Mr Anthony Jesurasa	Consultant Neurosurgeon, University Hospital of Wales, Heath Park Way, Cardiff, CF14 4XW Email: arjesurasa@doctors.org.uk
Principal Investigator	Mr Aprajay Golash	Department of Neurosurgery, Royal Preston Hospital, Sharoe Green Lane, Preston, PR2 9HT
Principal Invesitagor	Mr Gordan Grahovac	King's College Hospital, Denmark Hill, London, SE5 9RS
Neurosurgical Expertise	Mr Sashin Ahuja	Department of Spinal Surgery, University Hospital of Wales, Heath Park Way, Cardiff, CF14 4XW Email: sashinahuja@gmail.com
Service and Patient Representative	Ellen Sarewitz	Goffin Consultancy Riding House, Bossingham Road, Canterbury, CT4 6AZ Tel: +44 (0)1227 709220
Principal Investigator	Prof. David Choi	Consultant Neurosurgeon University College London Hospitals NHS

		Foundation Trust, 250 Euston Road, London, NW1 2PG Telephone: +44(0) 20 3448 3395/ 0845 155 5000 Email: d.choi@ucl.ac.uk
Principal Investigator	Prof. Nasir A. Quraishi	Consultant Spine Surgeon & Honorary Professor Centre for Spinal Studies & Surgery, Queen's Medical Centre, Derby Road, Nottingham, NG7 2UH, UK Tel: 0115 924 9924 ext. 83215 Email: nasir.quraishi@nuh.nhs.uk
Principal Investigator	Mr Alexander Montgomery	Consultant Spinal Surgeon, The Royal London Hospital, Whitechapel High Street, London E1 1FR Tel: 07951925354 Email: alexander.montgomery@nhs.net
Co-Principal Investigator	Mr Jonathan Bull	Consultant Neurosurgeon The Royal London Hospital, Whitechapel High Street, London, E1 1FR Email: jonathan.bull1@nhs.net
Principal Investigator	Mr Kia Rezjool	Consultant Neurological and Spinal Surgeon, Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, HA7 4LP Tel: 0208 909 5800 Email: k.rezajooi@nhs.net
Neurology and Rehabilitation Experience	Prof. Armin Curt	Balgrist University Hospital, Zurcih, Switzerland
TSC Members		
Clinical Trials Expertise	Prof. David Mendelow	Emeritus Professor Neurosurgery, University of Newcastle Email: amendelow@gmail.com
Chief Investigator	Dr Mark Kotter	Honorary Consultant in Neurosurgery Dept. of Clinical Neurosciences, Level 5, A Block, Addenbrooke's Hospital, Cambridge Biomedical Campus, Cambridge, CB2 0QQ Telephone: +44 1223 596029 Email: mrk25@cam.ac.uk
Independent Science and Service Expertise	Dr Timothy Boerger	Post-Doctoral Research Fellow Medical College of Wisconsin 3870 N 88th St, Milwaukee, WI, 53222 Tel: (USA) 262-365-8851 Email: Boergertf@gmail.com
Pain Medicine Representative	Prof. Abdul-Gaaliq Lalhen	Pain Consultant, Salford Royal NHS Foundation Trust, Stott Lane, M6 8HD Prof. Pain Medicine, Manchester Metropolitan University Email: abdul.lalkhen@gmail.com

Trial Statistician	Dr Kath Lowery	8 Armistead Way Cranage, Crewe, Cheshire, CW4 8FE. Email: kath.lowery@klxconsulting.com
Health Economist	Dr Matthew Glover	Leggett Building, University of Surrey, Guildford, Surrey, GU2 7XH, UK Email: matthew.glover@surrey.ac.uk
Orthopaedic Surgery / Clinical Trials Expertise	Mr Stephen McDonnell	Dep. Orthopaedic Surgery University of Cambridge sm2089@cam.ac.uk
Independent Ethical Expertise and Service Representative	Mrs Helen Wood	Chair of Trustees, Myelopathy.org Lay Member of Bromley, NHS Regional Ethics Committee Email: helen@myelopathy.org
DMC Members		
Chair	Prof. Michael Fehlings	Krembil Chair in Neural Repair & Regeneration University of Toronto, Toronto Western Hospital, 399 Bathurst St., WW 4-437, Toronto, ON M5T 2S8 Telephone: +1 (416) 603-5627 Email: michael.fehlings@uhn.ca
Independent Trial Statistician	Dr Michael Grayling	Research Fellow in Biostatistics Population Health Sciences Institute, Baddiley-Clark Building, Richardson Road, Newcastle upon Tyne NE2 4AX Email: Michael.Grayling@newcastle.ac.uk
Independent Clinical Trial Expertise	Prof Jeremy Fairbank	Retired Consultant Spinal Surgeon University of Oxford Email: jeremy.fairbank@gtc.ox.ac.uk

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3 Abbreviations

AE/AR	Adverse event/Adverse Reaction
ASA	American Society of Anesthesiologists physical status classification system
BPI	Brief Pain Inventory – Short Form
CA	Competent Authority
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CTIMP	Clinical Trial of Investigational Medicinal Product
DCM	Degenerative Cervical Myelopathy
DMC	Data Monitoring Committee
DN4	Douleur Neuropathique 4
DSUR	Development Safety Update Report
GAD7	Generalised Anxiety Disorder Questionnaire 7
GP	General Practitioner
GCP	Good Clinical Practice
HTA	Health Technology Assessment
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
Lami	Laminectomy alone
LamiF	Laminectomy and Fusion
MHRA	Medicines and Healthcare products Regulatory Agency
MCID	Minimum Clinically Important Difference
mJOA	Modified Japanese Orthopaedic Association
MRI	Magnetic Resonance Imaging
NDI	Neck Disability Index
NHS	National Health Service
NIHR	National Institute for Health Research
NIMP	Non Investigational Medicinal Product
OPLL	Ossification Posterior Longitudinal Ligament
PHQ9	Patient Health Questionnaire 9
PE	Pulmonary Embolus
PIS	Participant Information Sheet
R&D	Research and Development
RA	Regulatory Agency
REC	Research Ethics Committee
SAE/SAR	Serious Adverse Event/Serious Adverse Reaction
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
VTE	Venous Thromboembolism

4 Trial Synopsis

Title of clinical trial	**PO**sterior **L**aminectomy and **FIX**ation for **D**egenerative **C**ervical **M**yelopathy **[POLYFIX-DCM]**
Sponsor name	Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge
Medical condition or disease under investigation	Degenerative Cervical Myelopathy (DCM)
Purpose of clinical trial	To define best practice in the use of posterior spinal fixation for individuals undergoing multi-level posterior surgery for DCM
Primary objective:	To determine the mean difference by the modified Japanese Orthopaedic Association score at 24 months post-surgery of laminectomy and fusion and laminectomy alone, for multi-level DCM.
Exploratory outcomes:	1. To compare pain, physical function, quality of life, spinal alignment and adverse events between the two arms. 2. To undertake a detailed economic evaluation of laminectomy and fusion and laminectomy alone for multi-level DCM.
Trial Design	Multi-centre, pragmatic, randomised control trial
Trial Outcome Measures	**Primary outcome measure [24 Months]:** • Modified Japanese Orthopaedic Association score (mJOA) **Secondary outcome measures:** • VAS pain • SF36v2 (Quality of Life) Score (Physical Component Score, Mental Component Score and Bodily Pain) • EQ5D-5L • Neck Disability Index (NDI) • Brief Pain Inventory (BPI) • Douleur Neuropathique 4 (DN4) • Michigan Body Map (Pain Location) • Procedural complications, including intraoperative blood loss, dural tear, surgical site infection, wound breakdown and instrument failure • Adverse Events • Length of Hospital Stay

	• Length of Operation • Discharge Destination • Cervical, Dynamic X-Rays (Alignment [C2–7 lordosis, C2–7 Sagittal Vertical Axis and T1 slope], Fusion, Movement) • Myelopathy.org symptom inventory Assessments will be performed at 6, 12 and 24 months post-operatively.
Sample Size	Recruitment of 394 participants in total (40 in an internal pilot)
Summary of eligibility criteria	*Inclusion Criteria:* • Adult patients (aged 18 years or over) • Diagnosis of DCM • Scheduled for surgery involving 2 or more laminae • Able to provide informed consent • Able to read and understand English *Exclusion Criteria:* • Mild, non-progressive DCM (defined as a mJOA Score of >16) • Presentation in the context of acute trauma
Intervention	Multi-level posterior cervical spine surgical decompression with posterior fusion (screws and rods)
Comparator	Multi-level posterior cervical decompression alone (laminectomy)

Procedures: Screening & enrolment	• Age
	• mJOA
	• Planned Surgical Intervention
	• DCM characteristics
	  ○ Symptoms
	  ○ Length of DCM symptoms
	  ○ MRI image findings
	  ▪ Number of cervical spine levels for treatment
	• Neurological examination

Pre-operative Baseline assessment	• Weight (Kg) • Smoking status • Psychiatric comorbidities • Impaired gait • Medical History (Co-Morbidities) • Medication History • mJOA assessment

	• SF36v2 (quality of life) score (physical component score and mental component score) • EQ5D-5L • Patient Health Questionnaire (PHQ9) • Generalised Anxiety Disorder Questionnaire (GAD7) • Neck Disability index (NDI) • Brief Pain Inventory (BPI) • Douleur Neuropathique 4 (DN4) • Michigan Body Map (pain location) • Cervical X-Rays (Deformity, Auto-fusion, Movement) • Myelopathy.org symptom inventory • (Updated) Charleston Comorbidity Index • Healthcare Resource Use Questionnaire

Intra-operative assessment	• Operation title
	• Levels treated
	• American Society Anaesthesiology (ASA) grade
	• Operation Duration
	• Estimated Blood Loss
	• Intra-operative complications
	• Use of
	  ○ Intra-operative Navigation
	  ○ Intra-operative Neuromonitoring (neurophysiology)
	• Nature of Inserted Metalwork (if applicable)
	• Use of synthetic products to support fusion

Post-operative assessment on discharge	• Length of Stay and Ward Type • Complications (including surgical site infection, wound breakdown, post-operative infection, post-operative medical complication e.g. PE) • Other adverse events (E.g. blood transfusion) • Change in Medication • Cervical X-Rays
Follow up assessment at 6 months post-surgery	• mJOA • SF36v2 (Quality of life) Score • EQ5D-5L • Neck Disability Index (NDI) • Brief Pain Inventory (BPI) • Douleur Neuropathique 4(DN4) • Michigan Body Map (Pain Location)

	• Complications (including surgical site infection, wound breakdown, instrument failure) • Adverse Events • Cervical X-Rays • Myelopathy.org symptom inventory • Change in Medication • Healthcare Resource Use Questionnaire
Follow up assessment at 12 months post-surgery	• mJOA • SF36v2 (Quality of life) Score • EQ5D-5L • Neck Disability Index (NDI) • Brief Pain Inventory (BPI) • Douleur Neuropathique 4(DN4) • Michigan Body Map (Pain Location) • Complications (including surgical site infection, wound breakdown, instrument failure) • Adverse Events • Cervical X-Rays • Myelopathy.org symptom inventory • Change in Medication • Healthcare Resource Use Questionnaire • MRI cervical spine
Follow up assessment at 24 months post-surgery	• mJOA • SF36v2 (Quality of life) Score • EQ5D-5L • Neck Disability Index (NDI) • Brief Pain Inventory (BPI) • Douleur Neuropathique 4(DN4) • Michigan Body Map (Pain Location) • Complications (including surgical site infection, wound breakdown, instrument failure) • Adverse Events • Cervical X-Rays • Myelopathy.org symptom inventory • Change in Medication • Healthcare Resource Usage Questionnaire
End of trial	Participants involvement in the trial will end upon completion of the 24-month follow up following surgery. Any SAEs which have not resolved will be clinically followed up until resolution outside of this trial.
Procedures for safety monitoring during trial	All results will be forwarded to the DMC who will address safety issues. Any significant

	adverse results will be reported to the DMC via the Trial Coordinating Centre. Onward reporting to the TSC and Sponsor.
Criteria for withdrawal of participants	A participant may withdraw their consent at any time. Participants may also be withdrawn at the discretion of the Investigator or Sponsor, for the following reasons: • Significant protocol deviation; • An adverse event which results in inability to comply with trial procedures; • Degenerative Cervical Myelopathy disease activity, which results in inability to continue to comply with trial procedures.

4 Lay Summary

Degenerative Cervical Myelopathy [DCM] is a common condition caused when arthritic changes in the neck compress the spinal cord. It affects up to 2% of adults and causes numb and clumsy hands, imbalance, and bladder problems. Often it continues to worsen with time and left untreated lead to severe disability and paralysis.

The only current treatment is surgery, and a number of different operations are used. The aim of surgery is to create space for the spinal cord. Surgery is able to stop further deterioration and lead to some improvements.

For people who need DCM surgery from the back of their neck, the pressure on the spinal cord is relieved by removing part of the bone that surrounds the spinal cord called the laminae. This procedure on its own is called a ***laminectomy***. In some cases, metal implants are placed in addition to the laminectomy in order to stiffen the spine. This is called ***laminectomy and fusion***.

Both procedures have potential advantages and disadvantages.

Laminectomy alone is a more straightforward and shorter surgery, that does not affect the range of movement in the neck. However, without fusion a change in the alignment of the spine, called deformity may develop. Some surgeons believe deformity may affect long-term recovery and may cause greater neck pain for some people.

Laminectomy and fusion aims to prevent this deformity, but in doing so will greatly reduce the range of movement in the neck (particularly looking over the left or right shoulder). Some people find this a problem for everyday life, such as driving. Furthermore, the insertion of metal work slightly increases the risks of the surgery, whilst greatly increasing the cost.

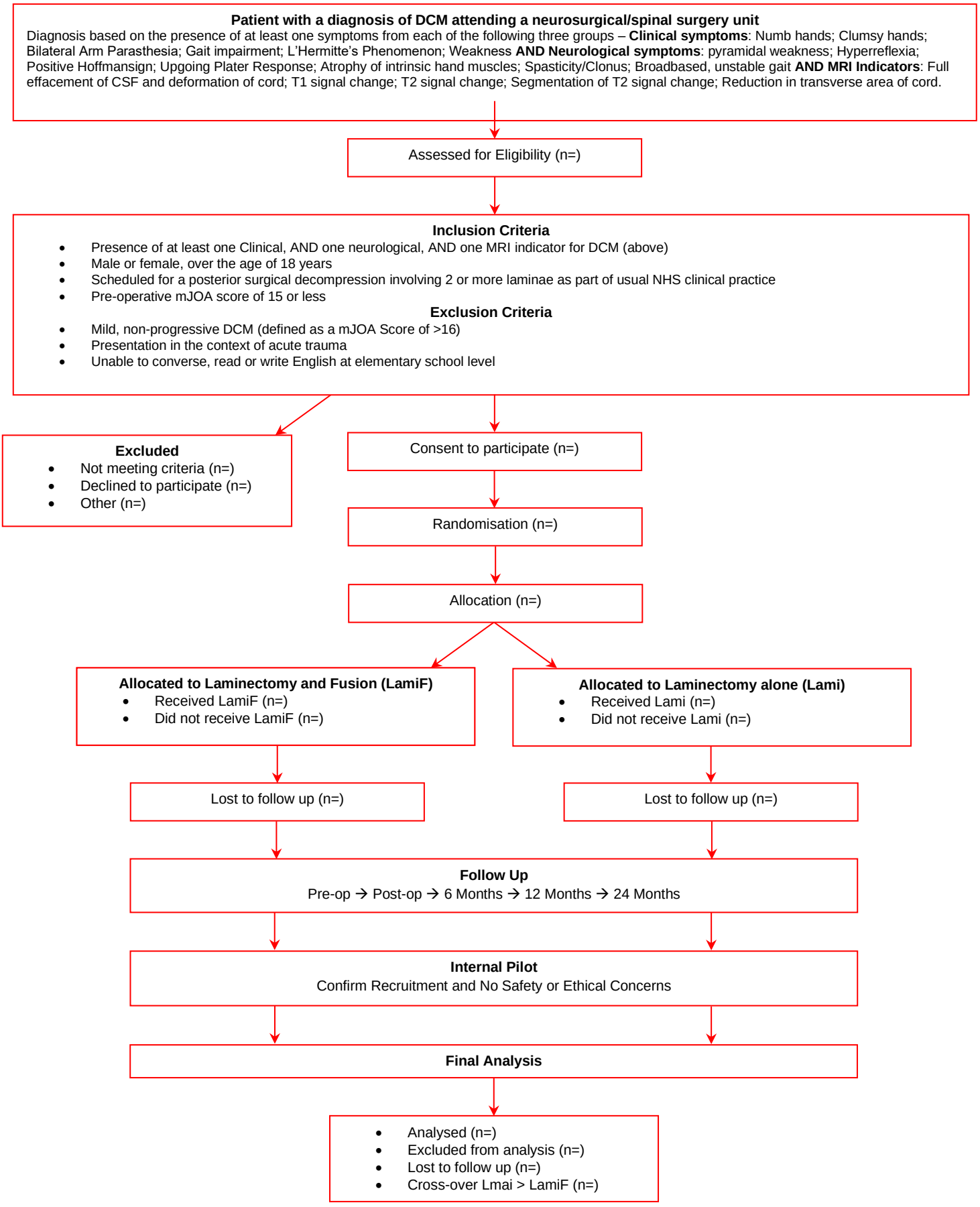
At present we do not know which of these approaches is better. Surgeons advocating for one or the other approach are split approximately half and half. Finding out whether one approach is superior is an important research priority, according to both patients and professionals.

We propose to address the following question, using a randomised controlled trial:

'Does laminectomy alone or laminectomy with fusion lead to better recovery in patients undergoing surgery for DCM from the back'?

Patients scheduled to undergo posterior surgery for DCM will be allocated using a computer to one or other treatment. This will involve 394 patients across 30+ sites, mainly based in the UK. Overall, it is designed to enable a better understanding and better choices with regards to surgery for this condition.

5 Trial Flow Chart



6 Introduction

6.1 Background

Degenerative cervical myelopathy (DCM) is the most common cause of spinal cord dysfunction in adults and is associated with a significantly reduced quality of life[1,2]. DCM results from compression of the spinal cord from surrounding structures due to chronic degenerative changes[3]. Compression may be anterior, posterior or both. DCM may occur as either single-level (at one vertebral level) or multi-level (two or more vertebral levels) disease. Patients commonly present with progressive neurological deficits, such as numb and clumsy hands, imbalance, frequent falls, loss of mobility and urinary incontinence[3], complemented by magnetic resonance imaging (MRI) changes. Patients may also present asymptomatically following an incidental finding on MRI or following an acute exacerbation of these symptoms[4–6]. Whilst DCM can remain mild and stable, the injury and disability often progresses with time. In these instances if left unchecked or undiagnosed, symptoms may progress to complete paralysis[7].

The incidence of DCM is estimated to be at 4/100,000 population/year[8]. However, this is likely a major under-estimation, as it is based on the occurrence of surgery which is not required in all cases,and cannot account for underdiagnosis. In a case series of patients presenting with neck of femur fracture, 18% had undiagnosed DCM[8]. Studies have shown that up to 26% of adults suffer from asymptomatic compression of the spinal cord, and this becomes more common with age. Further a proportion of these patients, estimated at 23%, will go onto develop symptoms within 4 years[4–6,9]. This would equate to an approximate prevalence of 1 in 50 adults. DCM is already estimated to be the most common cause of spinal dysfunction worldwide and with an aging population, both its incidence and prevalence are set to rise[3,10].

International guidelines advise prompt surgical decompression for the treatment of moderate to severe or progressive DCM[2]. Surgery aims to alleviate spinal cord compression in an attempt to prevent further neurological damage[11,12]. However, recovery after surgery is typically incomplete, with many patients left unable to work and function independently[1,11,13].

A number of different surgical techniques are used to treat DCM. These are broadly categorised as:

(1) Anterior or Posterior, depending on the approach to the spine (front or back of the neck).
(2) Instrumented or Non-instrumented, depending on whether metal implants alongside decompression are used or not, with the aim to form ‘fix’ the spine, by providing a cast to enable fusion of the bone.

Currently the choice of surgical procedure is left at the discretion of the treating surgeon, and there is variation in practice[14]. The choice of whether to use an anterior or posterior procedure is commonly informed by the location and type of spinal cord compression[15]. For example, spinal cord compression in front of the spinal cord is often treated using anterior surgery[16]. A recent RCT of anterior vs posterior surgery found they were equally effective[17]. Of note in this study, no patients treated posteriorly underwent a laminectomy alone.

For DCM treated posteriorly, the decompression is often called a laminectomy as the posterior elements of the spine are removed, including the posterior portion of the spine called the laminae. The consequent disruption to the spinal anatomy can have implications for its biomechanical function, leading to abnormal movements ('instability) or abnormal alignment ('deformity')[18]. The magnitude and likelihood of the changes increase with the number of consecutive levels operated on, i.e. posterior treatment for 'Multi-Level' DCM[19]. Consequently, some surgeons advocate stabilising the spine (laminectomy and instrumented fusion) as well as performing a decompression.

Whether or not this is significant to patients is uncertain[20,21], with conflicting evidence[19,22–24] and recommendations[25–28] leading to widespread variation in clinical practice[11,29]. Although widely used, there has been no prospectively powered comparison of these techniques.

The rationale for laminectomy and fusion

It is recognised that without stabilising techniques, such as instrumented fusion, 6–46% individuals undergoing multi-level posterior surgery may develop deformity in the form of kyphosis (abnormal forward curvature) of the cervical spine[19,30]. Some consider this relevant to patient outcomes in two principal ways:

1) Kyphosis affects posture and movement of the neck, impacting function and quality of life[18,31,32].
2) Ongoing instability can allow dynamic injury (injury to the spinal cord because the spine is too mobile, despite decompression) to persist, leading to late deterioration [22,23,33,34].

In keeping with this, studies have shown poorer functional outcomes, including late deterioration (10–37%) in patients without the use of stabilising techniques[20,22,33].

Further, it has been hypothesized that without stabilisation, the instability of spine may drive further arthritic changes leading to additional or recurrent spinal cord compression in untreated areas[22,35–37].

The rationale for decompression alone

However other studies have concluded that stabilising techniques are not required, as they do not change patient outcomes such as function or quality of life[38–42]. Given laminectomy and fusion significantly adds to the cost of treatment, including the implant costs and operative time, instrumentation has been questioned. It is also worth noting, that the insertion of stabilising techniques requires an additional skillset, moving it outside of the scope of non-specialist surgeons, holding implications for the delivery of care.

The present uncertainty is therefore likely driven by the paucity of clinical evidence and has led to the commissioning of POLYFIX DCM by the NIHR HTA, specifically to determine whether patients with multi-level DCM, treated posteriorly, benefit from additional instrumented fusion ('laminectomy and fusion') compared to decompression ('laminectomy') alone. POLYFIX DCM will be the first, adequately powered, randomised trial in response to this question.

7 Rationale for Trial

Degenerative Cervical Myelopathy is increasingly common and almost universally disabling.

DCM is the commonest form of adult spinal cord dysfunction[2], estimated to affect 1 in 50 adults[43]. Currently a minority of less than 5% of patients make a full recovery[11]. Therefore, most individuals with DCM undergoing surgery will suffer from life-long disability. A recent comparative study found that DCM sufferers have amongst the worst quality of life scores of all chronic disease[2]. A survey by Myelopathy.org (Charity No 1178673) of its DCM community found all patients harbour disabilities despite treatment with ~50% unable to work and ~50% dependent on others for day to day care[44,45]. This equates to an average lifetime loss of earnings for those of working age of £0.5m[46]. *Advances that improve outcomes are urgently required.*

Treatment is limited to surgery, and in particular for multi-level DCM, most commonly either laminectomy or laminectomy with fusion surgery

Surgery to decompress the spinal cord is the only evidence-based treatment for DCM [8]. Particularly in the UK, the two main options are laminectomy alone and laminectomy and fusion[47].

A secondary analysis of existing DCM trials suggests a possible neuromuscular benefit to instrumented fusion for multi-level DCM

In a secondary analysis of the AOSpine North America[12,48] and International observational studies[11], the world's largest trial dataset on DCM, instrumented fusion demonstrated significant benefit for patients with regards to pain, quality of life, and neurological function for multi-level disease. Specifically, patients undergoing laminectomy with instrumented fusion (N=186) had a significantly longer operative duration (P<0.0001, 231.44 vs 107.10 minutes) but a comparable length of hospital stay as compared to individuals treated with laminectomy only (N=22). In terms of outcomes, patients treated with laminectomy with fusion exhibited clinically meaningful improvements as measured with the best validated clinical tool the modified Japanese Orthopaedic Association Score (ΔmJOA=2.48) and the Nurick score (ΔNurick=1.19), whereas those who underwent a laminectomy without fusion did not (ΔmJOA=0.78; ΔNurick=0.29). There were significant differences between surgical cohorts in the change in mJOA and Nurick scores from preoperative to 24- months postoperative (mJOA: -1.70, p=0.0266; Nurick: -0.90, p=0.0241). The rate of perioperative complications was comparable (p=0.879). This data requires external validation but indicates that *laminectomy with fusion may improve outcomes in DCM*.

The demand for DCM surgery is rising and the cost-effectiveness of relative techniques unknown

Given the association with age, DCM prevalence is on the rise in the ageing populations of the developed world. This is reflected by year on year increases in the number of operations[49–51], including the NHS[52]. The average age of these patients undergoing surgery is increasing[49]. Its disabling clinical impact is of particular concern for the elderly[53], leading to reduced mobility and frailty through gait disturbance and imbalance[8,54]. NHS England recognises 1) reducing premature mortality and 2) enhancing quality of life for people with long-term conditions as important. Despite increasing age, older patients have been shown to experience the same absolute

benefit from surgery as younger patients[53]. Furthermore, older patients were found to be more likely to undergo posterior surgery, involving a greater number of levels[53].

Adult spinal deformity surgery has been shown to have higher total cost per quality-adjusted life year gained in the short term in comparison to other spinal procedures such as lumbar decompression[50]. Therefore, minimising risk of deformity, secondary to surgery for multilevel DCM, is going to become increasingly more important in financially pressured health care systems. Patil et al. highlighted the increasing financial burden associated DCM surgery, showing inflation-adjusted hospital charges rose by 48% for DCM surgery over a 10-year time period in the USA[49].

The first GIRFT (Get it right first time) Report in Spinal Surgery[55] recognised the significant expenditure faced by Spinal Surgery for surgical implants. Instrumentation is becoming increasingly favoured in spinal surgery[52]. This re-emphasises the cost-implications of instrumented fusion for DCM, and the requirement to understand its cost-effectiveness[56]. If instrumented fusion offers no additional benefit, it would represent a major cost saving for the NHS. In their evaluation of US practice during the 1990s, Deyo et al[57] identified a three-fold increase in spinal fusion correlating with the advent of new surgical devices and not necessarily evidence. Treatment of cervical spondylosis, including DCM, is the third leading area of healthcare expenditure in the US after diabetes and heart disease[58]. *Ensuring cost-effective spinal surgery is essential to meet ongoing demands.*

Consequently, establishing the optimal surgical management for cases of multi-level DCM treated posteriorly remains an unmet clinical need, with implications for both the patients and healthcare providers.

POLYFIX DCM will therefore address the following hypothesis:

Laminectomy and fusion improves outcomes following surgery for multi-level degenerative cervical myelopathy when compared to laminectomy alone.

P: Population

Adult patients with moderate to severe DCM, scheduled for posterior decompression surgery involving removal of 2 or more consecutive laminae.

I: Intervention

Laminectomy with instrumented fusion.

C: Comparison group

Laminectomy alone.

O: Outcome of interest

mJOA at 24 months post-surgery.

8 Trial Design

8.1 Statement of Design

POLYFIX DCM Will be a multi-centre pragmatic, randomised trial, with blinded outcome assessment, aiming to determine the comparative clinical- and cost-effectiveness of decompression and fusion, with decompression alone for multi-level DCM treated posteriorly. Due to the nature of the trial, the local clinical teams, patients and carers cannot be blinded to allocation. However, by employing centralised telephone follow-up, a blinded assessment of the primary outcome can be performed.

We have opted to detect a mean difference of 1 point on the mJOA, on the basis both surgical procedures are considered to achieve the minimally clinical important difference (MCID) (see below), and the aim here is to establish superiority of one technique (or not) over the other.

The trial will be preceded by an internal pilot in order to confirm recruitment, randomisation, treatment, and follow-up assessments (See Interim Analysis, 16.2).

8.2 Number of Centres

This is a multi-centre study involving approximately 20-30 sites in the UK and 5-10 sites internationally. The internal pilot phase will take place across approximately 10 UK sites. We have estimated annual, per site recruitment at 4-8 patients.

8.3 Number of Participants

We plan to include 394 participants in this trial, accounting for 10% attrition. The pilot phase aims to assess at least 40 participants.

In anticipation of requirements to optimise recruitment processes. We propose initially 3 patient focus groups of 3-6 people (1 within pilot phase, 2 within the substantive phase) conducted online using Zoom or equivalent videoconferencing system. These are planned to be conducted by Elen Sarewitz, a person with DCM who has expertise in identifying and responding to recruitment challenges in healthcare trials, but alternatively a suitably qualified alternative member of the investigating team could be used. Participants will be selected after they have made an enrolment decision. These workshops will focus on understanding individual experiences and are not designed to change their opinions. This will be supplemented with telephone, or face to face interviews of local investigators (<25) to explore their experiences of barriers to recruitment. Face to face interviews may make use of conferences, or site visits. The number and frequency of interviews will be responsive to challenges encountered and may therefore increase or decrease. Participation will be voluntary.

8.4 Participants Trial Duration

On average patients wait 79 days to undergo surgical treatment (NHS Hospital Episode Statistics, Pre-COVID19). Therefore, incorporating 24 months follow up atop of the average 2-3 months lead time to surgery, participants will be within trial for approximately 27 months.

8.5 Trial Objectives

8.5.1 Primary objective

- To detect a mean difference of 1 point in the mJOA scale at 24 months post-surgery between the laminectomy alone group and the laminectomy and fusion group

8.5.2 Secondary objectives

- Compare the short-term clinical effectiveness of laminectomy and laminectomy and fusion at 12 months post-surgery
- Compare pain, quality of life, surgical complications, and radiological measures between the two groups
- Undertake a detailed economic analysis
- Undertake a predefined secondary analysis of:
    - Number of levels treated
    - Presence / Amount of movement pre-operatively (>1mm subluxation on flexion/extension X-Ray)
    - Presence of auto-fusion at 1 or more cervical level pre-operatively[60] (radiological evidence of spontaneous fusion between two adjacent vertebrae)
    - Presence of Kyphosis (C2-C7 Cobb Angle <0°)[61]
    - Presence of Cervical Ossification of Posterior Longitudinal Ligament
    - Previous Cervical Spine Surgery
    - Age
- Undertake a predefined subgroup analysis of
    - Participants satisfying the criteria of modified K Line Negative, on pre-operative imaging[16,62]

8.6 Trial Outcome Measures

8.6.1 Primary outcome measure

The primary outcome measure for this trial is the modified Japanese Orthopaedic Association Score (mJOA).

This will be conducted by telephone, by a suitably trained professional, blinded to the participants allocation. Patients will be informed of this at screening assessment and in writing via the PIS.

The mJOA is an 18-point professional administered scale (0 worst to 18 best), which evaluates motor dysfunction in upper and lower extremities, loss of sensation and sphincter dysfunction. The mJOA is the international standard, and most validated measure for assessment of function in DCM[2,63,64].
Whilst laminectomy with fusion is hypothesized to improve both pain and neuromuscular function, a single validated endpoint for use in English speaking populations, encompassing assessment of both domains does not exist for DCM.

Pragmatically, the mJOA was therefore selected as the single primary end-point, on the basis:

(1) The recovery priorities for patients are pain, hand and walking function[65]

(2) The mJOA is the international standard, and most validated measure for assessment of neuromuscular function in DCM.[2,63,64] It has been the primary endpoint for most leading trials (AO Spine North America, AO Spine International, CSM Protect, CSM Surgery and RECEDE Myelopathy). It primarily evaluates motor dysfunction in upper and lower extremities but also altered sensation (including pain) to the hand(s) and sphincter dysfunction.
(3) Pain is a complex experience, and a single pain outcome tool has not been specifically validated for use in DCM
(4) The NIHR HTA (Funder) favoured a single primary end point (vs. co-primary end point)
(5) Although traditionally a clinician administered score, a version has now been developed for use remotely[66], potentially more conducive to current NHS practice due to the COVID19 pandemic.

Together therefore the mJOA targets hand and walking function (2 of the 3 recover priorities for patients), with some reference to pain. Further it is the best validated disease score, with established MCID and precedent across a number of DCM clinical trials.

Further it has been validated for remote assessment, and is therefore suitable for centralised and blinded outcome assessment by telephone[66–68].

8.6.2 Secondary outcome measures

The following outcomes will be measured after surgery:

- Length of Hospital Stay
- Length of Operation

The following outcomes will be measured at 6-, 12- and 24-months post-surgery:

- SF36v2 (Quality of life) Score
- EQ5D-5L
- Neck Disability Index (NDI)
- Brief Pain Inventory (BPI)
- Douleur Neuropathique 4(DN4)
- Michigan Body Map (Pain Location)
- Surgical Complications (Defined by Tetreault et al 2019[69])
- Other Adverse Events, including mortality
- Cervical X-Rays (Alignment [C2–7 lordosis, C2–7 Sagittal Vertical Axis and T1 slope], Fusion, Movement)

The following outcomes will be measured at 12 months:

- MRI Cervical Spine (Decompression, Cord Signal Intensity)

These outcomes have been selected to align with the newly completed Core Outcome Set for DCM, in the absence of defined core measurement set at the time of trial set-up[70].

Domain	Outcome	Polyfix Tools
Neuromuscular	Neck Mobility	NDI

	Finger Strength	mJOA
	Grip Strength	mJOA
	Finger/Hand Dexterity	mJOA
	Arm Weakness	mJOA
	Leg Weakness	mJOA
	Balance	mJOA
	Sensory Dysfunction	mJOA
	Bladder Dysfunction	mJOA
	Faecal Incontinence	SF36v2
Life Impact	Falls	EQ5D-5L
	Mobility	mJOA
		EQ5D-5L
		SF36v2
	Dependence	EQ5D-5L
		SF36v2
	Fatigue	EQ5D-5L
		SF36v2
	Mental Health	SF36v2
Pain	Location	Michigan Body Map
	Intensity	BPI
	Perception	BPI / DN4
	Pain Control	BPI
Radiology	Cord Compression	Post-Operative MRI
	Cord Signal Change	Post-Operative MRI
	Alignment	Post-Operative Cervical X-Rays
	Adjacent Segment Disease	Post-Operative MRI
Economic Impact	Employment Status	Healthcare Resource Use Questionnaire
	Cost of Care	Length of Stay
		Length of Operation
		Healthcare Resource Use Questionnaire
Adverse Events	Death	Other Adverse Effects
	Surgical complications	Surgical Complications[69]

With the exception of radiological outcomes (X-Ray and MRI Imaging), and an assessment of adverse events, including surgical complications, participants will be followed up using electronic or postal questionnaires ± telephone consultation. If the time point after an assessment exceeds 8 weeks, and there is no response, then the patient will be deemed as lost to that follow up.

8.6.3 Exploratory outcome measure

Further, this trial will invite participants to undertake digital assessments of finger, arm and leg function (See Appendix 4).

9 Selection and withdrawal of participants

9.1 Inclusion Criteria

To be included in the trial the participant must:

- Have given written informed consent to participate
- Be able to read and understand English
- Be aged 18 years and over
- Have a diagnosis of DCM, based on established criteria (see table below)
- Be scheduled for posterior surgery, involving 2 or more consecutive laminae

MRI Indicators	Clinical Symptoms	Neurological Signs
Effacement of CSF and deformation of cord%	Numb Hands	Pyramidal Weakness
T1 signal change	Clumsy Hands	Hyperreflexia
T2 Signal change	Bilateral Arm Paraesthesia	Positive Hoffman Sign
Segmentation of T2 signal change	Gait impairment	Upgoing Plantar Response
Reduction in transverse area of cord%	L'Hermitte's Phenomenon	Atrophy of intrinsic hand muscles
	Weakness	Spasticity/Clonus
If a patient is unable to undergo MRI (e.g. for an incompatible implant), a CT Myelogram compatible features are marked %		Broad based, unstable gait

9.2 Exclusion Criteria

The presence of any of the following will preclude participant inclusion:

- Mild and non-progressive DCM (defined as stable mJOA score >16 at two consecutive time points)
- Presentation in the context of acute trauma (e.g. central cord syndrome or spinal cord injury)

9.3 Treatment Assignment and Randomisation Number

An online randomisation system will be used to assign participants in a 1:1 ratio to treatment with either laminectomy alone or laminectomy and fusion. Stratified blocked randomisation will be used stratifying by baseline mJOA (<12vs>=12), age (<60 years vs >=60 years) and time to onset (>6 months vs <=6 months); random block size will be used.

9.4 Method of Blinding

Due to the nature of the trial, the clinical teams, patients and carers cannot be blinded to allocation. However, assessors of the primary endpoint (mJOA), can and will be blinded to participant allocation. This will be done centrally by a trained assessor. The same assessor will not be used for all cases.

9.5 Participant Withdrawal Criteria

Each patient has the right to withdraw from the trial at any time.

The investigator may discontinue a participant from the trial at any time if necessary and for reasons including the following:

- Significant non-compliance with treatment regimen or trial requirements
- An adverse event that requires discontinuation of treatment or results in inability to comply with trial procedure

Any data collected will remain in the trial and the patient will continue to be followed up unless consent is withdrawn. Patients who have been withdrawn from the trial will not be replaced as the power calculation for the trial allows for an 8% drop out rate.

All discontinuations and withdrawals will be documented in the CRF. If a patient wishes to discontinue, anonymised data collected up until that point will be included in the analysis.

10 Trial Treatments

The two surgical treatments to be compared in POLYFIX DCM are:

1. Laminectomy alone.
2. Laminectomy and fusion.

10.1 Treatment Summary

Both procedures are conducted under general anaesthesia, in the prone position. The head is typically supporting using a skull clamp (e.g. Mayfield ™ or Sugita ™).

Localisation of the spinal level to be operated on is usually based on anatomical markers. Intra-operative images may be obtained using fluoroscopy prior to ensure the correct levels are removed. This ensures the incision is correctly placed and not too long. Unless contraindicated, skin preparation should be with an alcoholic skin prep agent, care must be taken to avoid alcoholic skin preparations from running round into the eyes. Local anaesthetic with adrenaline is preferably used at the incision site.

10.1.1 Intervention: Laminectomy and fusion

Whilst individual techniques may vary slightly, the principles of a cervical laminectomy are as follows:

- The patient is positioned prone, and the correct spinal level is identified
- A midline incision is made and dissection is undertaken down to the spinous process.
- A subperiosteal dissection to expose the spinous process, lamina and lateral masses of the desired levels is then performed.
- Fluoroscopy may be obtained to ensure the correct levels are removed.

- A posterior cervical laminectomy is performed using one of the following techniques:
    - A high-speed cutting burr
    - A manual laminectomy using a combination of rongeurs and instruments

    - A footplate craniotome
- Instrumentation and fusion is performed.
    - Depending on the cervical level and surgeons' preference, either lateral mass screws or pedicle screws are inserted.
    - Appropriate length rods are then secured with set screws/caps.
    - Decortication is performed and bone graft material may be placed along the lateral mass edges bilaterally.
    - This can be supplemented or supported with synthetic products (E.g. Actifuse, Baxter)
- A subfascial drain can then be placed and the muscle, fascia and skin closed.

10.1.2 Comparison: Laminectomy alone

Whilst individual techniques may vary slightly, the principles of a cervical laminectomy are as follows:

- The patient is positioned prone and the correct spinal level is identified
- A midline incision is made and dissection is undertaken down to the spinous process.
- A subperiosteal dissection to expose the spinous process, lamina and lateral masses of the desired levels is then performed.
- Fluoroscopy may be obtained to ensure the correct levels are removed.

- A posterior cervical laminectomy is then performed using one of the following techniques:
    - A high-speed cutting burr
    - A manual laminectomy using a combination of rongeurs
    - A footplate craniotome
- A subfascial drain can then be placed and the muscle, fascia and skin closed.

A list of the known complications of both of the above procedures are detailed in section 12.3.

10.2 Surgeon Experience and Eligibility

Both techniques, laminectomy and laminectomy plus fusion, belong to the standard repertoire of any spine surgeon. However, laminectomy alone can also be conducted by general neurosurgeons. This is well recognised within the spinal centres in the UK. The NHS standard contract for complex spine surgery outlines the necessity for collaboration between generalist surgeons and complex spine surgeon with orthopaedic or neurosurgical background for the treatment of degenerative neck conditions[71].

Whilst research, including a large retrospective multicentre study of 675 patients has not demonstrated that surgeon experience changes outcomes in patients undergoing posterior surgery for DCM[72], to mitigate risks of variations in outcome due to surgeon experience, we propose to:

- Only accept study sites capable of delivering both operations,
- Site PIs should be competent in both operations AND
- Will be responsible for ensuring surgeons performing an operation are sufficiently experienced to do so. We propose this includes ensuring they have performed and/or supervised the procedure at least 5 times in the preceding 12 months

11 Procedures and assessments

11.1 Participant identification

Local investigatory teams will identify and approach potential participants at each participating centre. It is likely that most potential participants identification will occur in the outpatient setting.

11.2 Consent

The Informed Consent form must be approved by the REC and must be in compliance with GCP, local regulatory requirements and legal requirements. The investigator or designee must ensure that each trial participant, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with their participation.

The investigator or designee will obtain written informed consent from each participant or the participant's legally acceptable representative before any trial-specific activity is performed. The informed consent form used for this trial and any change made during the course of this trial, must be prospectively approved by the REC. The investigator will retain the original of each participant signed informed consent form.

Should a participant require a verbal translation of the trial documentation by a locally approved interpreter/translator, it is the responsibility of the individual investigator to use locally approved translators.

Any new information which becomes available, which might affect the participant's willingness to continue participating in the trial will be communicated to the participant as soon as possible.

11.3 Screening evaluation

Potential subjects will be approached at neurosurgery centres at each participating centre. Most trial assessments will take place in outpatient clinic during routine hospital attendance. MRI scans will take place at the local radiology department.

11.3.1 Screening Assessments

Potentially eligible patients with DCM will be approached by a delegated member of the local trial team and given a PIS to read in their own time. Patients will be offered the opportunity to ask questions, or advised to get in touch in order to address any questions that they may have on the contents of the PIS. If they decide to participate in the trial, they will undergo a screening assessment to confirm their eligibility for the trial as per inclusion/exclusion criteria described in section 9.1 and 9.2.

Screening assessments to establish eligibility will include:

- Age
- mJOA
- Planned Surgical Intervention
- DCM characteristics
    - Symptoms
    - Length of DCM symptoms
    - MRI image findings

    - Number of cervical spine levels for treatment
- Neurological examination

Estimated time: <30minutes.

An anonymised record of the patients approached along with the numbers of, and reasons for, screen failures and refusal of consent will be kept at each site on a screening log and reported to the Trial Co-ordinating Centre on a monthly basis. This information will be used to identify any barriers to recruitment and allow improvement measures to be identified and implemented in a timely manner.

11.3.2 Participant Registration/Randomisation

Following screening, eligible subjects will be randomised to either laminectomy and or laminectomy and fusion. They will then be given a unique trial ID number.

11.4 Baseline Assessments

All participants will have a full medical history taken and a clinical examination. The following data points are to be recorded:

- Weight in Kg
- Gender
- DCM characteristics
- Smoking status (yes/no)
- Psychiatric comorbidities (yes/no)
- Impaired gait (yes/no)
- Medical History (Co-Morbidities)
- Medication History
- mJOA assessment
- SF36v2 (quality of life) score (physical component score and mental component score)
- EQ5D-5L
- Patient Health Questionnaire (PHQ9)
- Generalised Anxiety Disorder Questionnaire (GAD7)
- Neck Disability index (NDI)
- Brief Pain Inventory (BPI)
- Douleur Neuropathique 4 (DN4)
- Michigan Body Map (pain location)
- Cervical X-Rays (Deformity, Auto-fusion, Movement)
- Myelopathy.org symptom inventory
- (Updated) Charleston Comorbidity Index[73]
- Healthcare Resource Use Questionnaire
- Optional assessments
    - MoveMed
    - Carer Quality of Life

Performed imaging, including the pre-existing MRI used for diagnosis and screening, will be centralised to further characterise the radiological features of a participants DCM, including cord compression and cervical spine alignment. The presence or absence of OPLL and on what basis (e.g., what form of imaging) was this determined, as this is relevant to the sensitivity of its detection, will however be recorded locally.

Estimated time: 45minutes.

11.5 Trial assessments

11.5.1 Timing of assessments

Post-operatively, participants are to be seen at their local hospital at 6-, 12- and 24-months post-surgery for assessments. Patients given additional consent, may also be followed up for an additional 60 ± 2 months, (5 years) subject to additional funding.

11.5.2 Intra-Operative Assessments

- Operation title
- Cervical Levels treated
- American Society Anaesthesiology (ASA) grade
- Operation Duration
- Estimated Blood Loss
- Intra-operative complications
- Use of
    - Intra-operative Navigation
    - Intra-operative Neuromonitoring (neurophysiology)
- Nature of Inserted Metalwork, if applicable (number / brand)
- Use of synthetic products to support fusion, e.g. Actifuse, Baxter.

Estimated time: 5minutes.

11.5.3 Post-Operative Assessments on Discharge

- Length of Stay and Ward Type
- Complications (including surgical site infection, wound breakdown, post-operative infection, post-operative medical complication e.g. PE)
- Other adverse events (E.g. requirement for blood transfusion)
- Change in Medication
- mJOA
- SF36v2
- EQ5D-5L
- NDI
- BPI
- DN4
- Michigan Body Map
- Cervical X-rays
- Optional
    - MoveMed
    - Carer Quality of Life

Estimated time: 15minutes.

11.5.4 Follow up Assessments at 6 months post-surgery (±21 days)

- mJOA
- SF36v2 (Quality of life) Score
- EQ5D-5L

- Neck Disability Index (NDI)
- Brief Pain Inventory (BPI)
- Douleur Neuropathique 4(DN4)
- Michigan Body Map (Pain Location)
- Complications (including surgical site infection, wound breakdown, instrument failure)
- Adverse Events
- Cervical X-Rays (Deformity, Fusion, Movement)
- Myelopathy.org symptom inventory
- Change in Medication
- Healthcare Resource Use Questionnaire
- Optional
    - MoveMed
    - Carer Quality of Life

Estimated time: 60minutes.

11.5.5 Follow up Assessments at 12 months post-surgery (±21 days)

- mJOA
- SF36v2 (Quality of life) Score
- EQ5D-5L
- Neck Disability Index (NDI)
- Brief Pain Inventory (BPI)
- Douleur Neuropathique 4(DN4)
- Michigan Body Map (Pain Location)
- Complications (including surgical site infection, wound breakdown, instrument failure)
- Adverse Events
- Cervical X-Rays (Deformity, Fusion, Movement)
- Myelopathy.org symptom inventory
- Change in Medication
- Healthcare Resource Use Questionnaire
- Optional
    - MoveMed
    - Carer Quality of Life

Estimated time: 60minutes.

- MRI Cervical Spine

A post-operative MRI Cervical Spine is performed by most, but not all surgeons, typically at 6-12 months. Therefore, as a secondary end, point this will be only be collected where performed.

Estimated time: 30 minutes.

11.5.6 Follow up Assessments at 24 months - end of trial visit (±21 days)

- mJOA
- SF36v2 (Quality of life) Score

- EQ5D-5L
- Neck Disability Index (NDI)
- Brief Pain Inventory (BPI)
- Douleur Neuropathique 4(DN4)
- Michigan Body Map (Pain Location)
- Complications (including surgical site infection, wound breakdown, instrument failure)
- Adverse Events
- Cervical X-Rays (Deformity, Fusion, Movement)
- Myelopathy.org symptom inventory
- Change in Medication
- Healthcare Resource Usage Questionnaire
- Optional
    - MoveMed
    - Carer Quality of Life

Estimated time: 60minutes.

11.5.7 Optional: Digital Endpoints, Continuous Monitoring

- MoveMed[74] [Appendix 4]

MoveMed is a new remote monitoring tool for DCM, developed in response to the patient demand for an ambulatory assessment. DCM patients report a significant variation in symptoms[75], which cannot be captured by single time point: "*one day you can walk, one day you can't*" and "*you look perfectly fine, you talk perfectly fine and all of a sudden y' you're on your back on the pavement and you can't get up again*"

MoveMed uses a compatible smart-phone to collect quantitative and sensitive measurements of hand, arm and leg function using a combination of interactive on screen tests, and activity monitoring using the phone's inbuilt sensors. Further information is detailed in Appendix 4.

MoveMed has received positive feedback, from testing in people with DCM and is being adopted into the Cambridge University Hospital, Spinal Cord Injury Pathway:

- *"This will enable you to get the whole picture of the disease, symptoms as a whole and not just a snapshot."*
- *"As no two days are the same it would be good to have a record of how symptoms are and seeing if things are degenerating with something to show to a doctor…. And not be told it's all in your head."*

MoveMed will be an optional end-point in this trial, and eligible only to patients with a compatible smartphone. This is estimated to be approximately 50% of participants[76]. A supplementary sheet will be provided to those interested, to complement their PIS.

11.5.8 Optional: Carer Quality of Life

The impact of a chronic condition such as DCM is not restricted to the patient, as their disability can have an impact on the well-being and health of those, they subsequently live and/or depend on. In a pilot study of individuals reporting to be informal carers of

people with DCM, we identified a reduced quality of life using a tool called the Carer QOL[77–80]. The Carer QOL has been designed, and extensively piloted across a range of cultures and languages. Measuring this impact has implications of health-economic outcomes and was a recommendation of the AO Spine RECODE-DCM Core Outcome Set.

Consequently, in this study, participants at baseline will be informed of option to measure CarerQOL and provided with a PIS to distribute to their informal carer(s). Contact details will be provided should the participant, or their informal carer(s) have follow up questions for the investigator team. Informal Carers consenting to participate will be sent a CarerQOL to complete at baseline, discharge from hospital, 6, 12 and 24 months after surgery.

11.5.9 Table of Outcome Measures

Outcome	**Timepoints**	**Assessor**	**Estimated Time to Complete (min)**
Age	Baseline	Local team	1
Gender	Baseline	Local team	1
Medical History	Baseline	Local team	5
Medication History	Baseline, 6-, 12- and 24-months post-operatively	Local Team	5
Charleston Comorbidity Index	Baseline	Local Team	1
DCM characteristics	Baseline	Local Team (Additional Central Analysis)	5 (*Baseline MRI will have already been performed)*
Neurological examination	Baseline	Local team	5
Myelopathy.org symptom inventory	Baseline, 6-, 12- and 24-months post-operatively	Patient	20
Smoking status	Baseline	Local team	1
Psychiatric comorbidities	Baseline	Local team	1
Impaired gait	Baseline	Local team	2
Weight	Baseline	Local team	1
mJOA	Baseline, 6-, 12- and 24-months post-operatively	Central Team	5
SF36v2	Baseline, 6-, 12- and 24-months post-operatively	Patient (Administered Centrally)	10
EQ5D-5L	Baseline, 6-, 12- and 24-months post-operatively	Patient (Administered Centrally)	5
NDI	Baseline, 6-, 12- and 24-months post-operatively	Patient (Administered Centrally)	5
BPI	Baseline, 6-, 12- and 24-months post-operatively	Patient (Administered Centrally)	5
PHQ9	Baseline	Patient	5

		(Administered Centrally)	
GAD7	Baseline	Patient (Administered Centrally)	5
DN4	Baseline, 6-, 12- and 24-months post-operatively	Local team	2
Michigan Body Map	Baseline, 6-, 12- and 24-months post-operatively	Patient (Administered Centrally)	3
Complications	Baseline, intra-operative, immediately post-operatively, 6-, 12- and 24-months post-operatively	Local team	1
Cervical X-Rays	Baseline, post-operatively, 6-, 12- and 24-months post-operatively	Local Team (Analysis, Central)	5
Adverse event assessments	Baseline, intra-operative, immediately post-operatively, 6-, 12- and 24-months post-operatively	Local team	1
MRI Cervical Spine	12-months Post-Operatively	Local Team (Analysis, Central)	30
Healthcare Resource Usage Questionnaire	Baseline, 6-, 12- and 24-months post-operatively	Patient (Administered Centrally)	10

Preferentially, patient reported outcome measures conducted centrally will be captured using an electronic (web-based) form, directly by the participant. However, at the choice of the participant (and able to change in response to their requirements throughout the trial) this could alternatively be conducted using a paper, postal questionnaire or via telephone.

11.6 Schedule of Assessments

** Optional*
§ Performed by Significant Other, with their consent, and optional
Centralised

Assessment	Screening	Randomisation	Pre-operative baseline	Surgery	Post-operatively / Discharge	6 months post operatively (±21 days)	12 months post operatively (±21 days)	24 months post operatively (±21 days)
Informed consent	X							
Age	X							
Gender			X					
Medical History			X					
Medication History/Review			X		X	X	X	X
Charleston Comorbidity Index			X					
DCM characteristics	X		X					
Neurological examination	X							
Myelopathy.org symptom inventory [MOSI]			X			X	X	X
Smoking status			X					
Psychiatric comorbidities			X					
Impaired gait			X					
Randomisation		X						
Weight			X					
mJOA	X		X		X	X	X	X
SF36v2			X		X	X	X	X
EQ5D-5L			X		X	X	X	X
NDI			X		X	X	X	X
BPI			X		X	X	X	X
DN4*			X		X	X	X	X
Michigan Body Map*			X		X	X	X	X
Healthcare Resource Usage Questionnaire			X			X	X	X
PHQ9*			X					
GAD7*			X					
Complications				X	X	X	X	X
Cervical X-Rays			X		X*	X	X*	X
Operation title				X				
ASA grade				X				

Cervical levels treated				X				
Operation Duration				X				
Intra-Operative Blood Loss				X				
Adverse event assessments				X	X	X	X	X
Treatment details (e.g. procedure, intraoperative adverse events, use of navigation and neuromonitoring; type of metalwork and synthetic products used)				X				
Length of stay and Level of Care				X				
MRI Cervical Spine*							X	
MoveMed*			X	X	X	X	X	X
Carer Quality of Life§			X		X	X	X	X

11.7 Long-Term Follow-up Assessments

Subject to additional funding, and the provision of optional consent, it is proposed to conduct long-term follow-up for up to 5 years, using a combination of data linkage, to NHS Digital Hospital Episode Statistics, and telephone or electronical / postal follow up.

This will principally evaluate:
(1) Healthcare Resource Usage (NHS Digital Linkage)
(2) mJOA (Neurological Disability)
(3) SF36 (Quality of Life)
(4) BPI and NDI (Pain / Neck Disability)

The frequency and nature of this will be confirmed in due course, but as a minimum would make use of NHS Digital Hospital Episode Statistics.

11.8 End of Trial Participation

Trial participation will end 24 months post-surgery for each participant (unless consent has been given, and funding secured, for extended follow up). Following trial completion, patients will return to routine care as per their local centre protocols.

11.9 Trial restrictions

Beyond the inclusion and exclusion criteria, there are no specific restrictions to participation in this trial.

12 Assessment of Safety

12.1 Definitions

12.1.1 Adverse event (AE)

Any untoward medical event in a participant of a clinical investigation which does not necessarily have a causal relationship to the intervention/treatment

An untoward medical event can include:

- any unintentional, unfavourable clinical sign or symptom
- any new illness or disease or the deterioration of existing condition
- any clinically relevant deterioration in any clinical tests

12.1.2 Adverse reaction (AR)

All untoward and unintended responses to the clinical investigation treatment. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the treatment qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

12.1.3 Unexpected adverse reaction

An adverse reaction, the nature, or severity of which is not consistent with the known

safety information of the /intervention/treatment under investigation.
When the outcome of the adverse reaction is not consistent with the applicable safety reference information (RSI) this adverse reaction should be considered as unexpected.

The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on participant /event outcome or action criteria.

12.1.4 Serious adverse event or serious adverse reaction (SAE / SAR)

Any untoward medical occurrence that:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect.
- is an important medical event - Some medical events may jeopardise the participant or may require an intervention to prevent one of the above characteristics/ consequences. Such events (hereinafter referred to as ‘important medical events’) should also be considered as ‘serious’

Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

12.2 Expected Adverse Reactions/Serious Adverse Reactions (AR /SARs)

The Health Research Authority (HRA) defines the terms **related** and **unexpected** as:

- **Related**: that is, it resulted from administration of any research procedures. All complications by definition are related to the trial procedures. (Untoward medical events which are unrelated to the trial procedures are not being collected in this trial.)

- **Unexpected:** that is, the type of event that in the opinion of the investigator is not considered expected. Examples of expected complications are provided in section 13.2; note this is not an exhaustive list.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see section 12.4 for Responsibilities). These characteristics / consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

12.3 Expected Adverse Events/Serious Adverse Events (AE/SAE)

The following is a list of expected complications related to the administration of any research procedure including pre- and post-operative complications associated with either surgical procedure or the use of general anaesthetic.

This are categorised as Common (>1/100), Uncommon (~1/1000) and Rare ~1/10,000

Common

- Dural tear
- CSF leak
- Epidural Haematoma
- Neurological root injury (including C5 Palsy)
- Worsening myelopathy
- Post-operative red eye
- Swallowing difficulties
- Hoarse Voice
- Neck Pain
- Adjacent segment disease
- Drowsiness, confusion or restlessness
- Nausea and/or vomiting
- Soft tissue infection
- Urinary tract infection
- Respiratory infection

Uncommon

- Inadequate Decompression
- Spinal cord injury
- Injury to the mouth or teeth from intubation or the breathing tube
- Myocardial Infarction
- Respiratory problems

Rare

- Blindness
- Vertebral artery injury
- Wrong level surgery
- Anaphylaxis
- Stroke
- Cardiac Arrest

For laminectomy only procedures, as outlined in the trial premise, post procedural deformity or instability is possible, but the frequency and significance will be defined by this trial.

For laminectomy and fusion, the insertion of metal work carries the following additional uncommon risks:

- Metal work malposition
- Metal work failure
- Failure of bony fusion

Whilst CRFs will document each adverse event specifically, it is planned that for analysis, this will be aggregated into the consensus derived categories of surgical complications for DCM, by Tetreault et al 2019 [69] .

12.4 Evaluation of adverse events

The Sponsor expects that adverse events are recorded from the point of Informed Consent regardless of whether a participant has yet received a research procedure. Individual adverse events should be evaluated by the investigator. This includes the evaluation of its seriousness, and any relationship between the investigational medicinal product(s) and/or concomitant therapy and the adverse event (causality).

12.4.1 Assessment of seriousness

Seriousness is assessed against the criteria in section 12.1.4.This defines whether the event is an adverse event, serious adverse event or a serious adverse reaction

12.4.2 Assessment of causality

Definitely: A causal relationship is clinically/biologically certain. **This is therefore an Adverse Reaction**

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the research procedure and there is a reasonable response on withdrawal. **This is therefore an Adverse Reaction.**

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the AE and administration of the research procedure **This is therefore an Adverse Reaction.**

Unlikely: A causal relation is improbable and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unrelated: A causal relationship can be definitely excluded and another documented cause of the AE is most plausible. **This is therefore an Adverse Event.**

Unlikely and Unrelated causalities are considered NOT to be related to the intervention
Definitely, Probable and Possible causalities are considered to be related to the intervention

A pre-existing condition must not be recorded as an AE or reported as an SAE unless the condition worsens during the trial and meets the criteria for reporting or recording in

the appropriate section of the CRF.

12.4.3 Clinical assessment of severity

Mild: The participant is aware of the event or symptom, but the event or symptom is easily tolerated

Moderate: The participant experiences sufficient discomfort to interfere with or reduce his or her usual level of activity

Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and / or the participant's life is at risk from the event.

12.4.4 Recording of adverse events

Adverse events and adverse reactions should be recorded in the medical notes and the appropriate section of the CRF and/or AE/AR log. Serious Adverse Events and Serious Adverse Reactions should be reported to the sponsor as detailed in section 12.5.

12.5 Reporting serious adverse events

Each Principal Investigator needs to record all adverse events and report serious adverse events to the Chief Investigator using the trial specific SAE form within 24 hours of their awareness of the event.

The Chief Investigator is responsible for ensuring the assessment of all SAEs for expectedness and relatedness is completed and the onward notification of all SAEs to the Sponsor immediately but not more than 24 hours of first notification. The sponsor has to keep detailed records of all SAEs reported to them by the trial team.

The Chief Investigator is also responsible for prompt reporting of all serious adverse event findings to the relevant authorities of each concerned Member State if they could:

- adversely affect the health of participants
- impact on the conduct of the trial
- alter the risk to benefit ratio of the trial

The completed SAE form can emailed. Details of where to report the SAE's can be found on the POLYFIX DCM SAE form and the front cover of the protocol.

12.6 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions which occur in the concerned trial, and that are both unexpected and serious (SUSARs) are subject to expedited reporting.

12.6.1 Who should report and whom to report to?

The Sponsor delegates the responsibility of notification of SUSARs to the Chief Investigator. The Chief Investigator must report all the relevant safety information previously described, to the:

- Sponsor
- Ethics Committee in the concerned member states

The Chief Investigator shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

12.6.2 When to report?

12.6.2.1 Fatal or life-threatening SUSARs

All parties listed in 12.6.1 must be notified as soon as possible but no later than **7 calendar days** after the trial team and Sponsor has first knowledge of the minimum criteria for expedited reporting.
In each case relevant follow-up information should be sought and a report completed as soon as possible. It should be communicated to all parties within an additional **8 calendar days**.

12.6.2.2 Non-fatal and non-life-threatening SUSARs

All other SUSARs and safety issues must be reported to all parties listed in 12.6.1 as soon as possible but no later than **15 calendar days** after first knowledge of the minimum criteria for expedited reporting. Further relevant follow-up information should be given as soon as possible.

12.6.3 How to report?

12.6.3.1 Minimum criteria for initial expedited reporting of SUSARs

Information on the final description and evaluation of an adverse reaction report may not be available within the required time frames for reporting. For regulatory purposes, initial expedited reports should be submitted within the time limits as soon as the minimum following criteria are met:
a) a suspected research procedure
b) an identifiable participant (e.g. trial participant code number)
c) an adverse event assessed as serious and unexpected, and for which there is a reasonable suspected causal relationship
d) an identifiable reporting source

and, when available and applicable:

-
- an unique case identification (i.e. sponsor's case identification number)

12.6.3.2 Follow-up reports of SUSARs

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. Further available relevant information should be reported as follow-up reports.
In certain cases, it may be appropriate to conduct follow-up of the long-term outcome of a particular reaction.

13 Evaluation of Results (Definitions and response/evaluation of outcome measures)

13.1 Response criteria

13.1.1 Neurological function

To be measured by the mJOA scale at baseline, 6-, 12- and 24-months post-surgery.

13.1.2 Pain

To be measured by the BPI, numeric rating score for average pain scale at baseline, 6-, 12- and 24-months post-surgery.

13.1.3 Radiological Outcomes

Cervical spine X-Rays (flexion/extension lateral views) will be conducted at baseline, post-operatively, 6-, 12- and 24-months post-surgery. Pre-operative X-Rays will assess any movement and alignment. Post-operative X-Rays will assess for alignment, fusion and movement.

13.1.4 Quality of life

Participant quality of life will be assessed at baseline, 6-, 12- and 24-months post-surgery. Both will be assessed by the SF36v2 survey.

14 Storage and Analysis of Samples

POLYFIX DCM will not involve neither the collection nor storage of any samples.

15 Statistics

15.1 Statistical methods

The primary objective will be evaluated using a two-sided t-test at a 5% significance level. The trial is powered to detect a 1-point difference in the mJOA scale between arms.

The ordering of subsequent endpoints for formal hypothesis testing will be:

1. BPI Pain
2. Neck Disability Index
3. PCS component of the SF-36
4. MCS component of the SF-36
5. mJOA (Upper Limb, Motor Score)
6. mJOA (Lower Limb, Motor Score)

A range of MCID for these endpoints have been proposed using a range of methods. As secondary endpoints the trial is not implicitly powered to detect a specific difference, and instead analysis will estimate the difference. However, in order to recognise what is considered meaningful in advance, the following MCID are agreed based on the available literature; BPI 20mm, NDI 8 points, SF36 PCS 5 points, MCS SF36 4 points, mJOA Subdomain scores 1 point[81–88].

A descriptive analysis of the following secondary outcome measures will be provided:

- SF36v2 (Quality of life) Score
- EQ5D-5L
- Neck Disability Index (NDI)
- Brief Pain Inventory (BPI)
- Douleur Neuropathique 4(DN4)
- Michigan Body Map (Pain Location)
- Complications (including surgical site infection, wound breakdown, instrument failure)
- Adverse Events

- Cervical X-Rays (Deformity, Fusion, Movement)
- Neurological examination
- Myelopathy.org Symptom Inventory

A predefined subgroup analysis of the following variables will take place:

- Number of levels treated
- Presence / Amount of movement pre-operatively (>1mm subluxation on flexion/extension X-Ray)
- Presence of auto-fusion at 1 or more cervical level pre-operatively[60] (radiological evidence of spontaneous fusion between two adjacent vertebrae)
- Presence of Kyphosis (C2-C7 Cobb Angle <0°)[61]
- Presence of Cervical Ossification of Posterior Longitudinal Ligament
- Previous Cervical Spine Surgery
- Age

The following baseline covariates, in addition to the baseline value of the endpoint, will be used to adjust all comparisons:

- Time to onset
- Smoking status (yes/no)
- Age
- Psychiatric comorbidities (yes/no)
- Impaired Gait (yes/no)

A detailed statistical analysis plan will be produced before the final data base lock.

15.2 Interim analyses

An interim analysis will be conducted at 9 months from first recruited patient (Pilot Phase), in order to confirm recruitment, randomisation, treatment, and follow-up assessments.

The progression criteria to the substantive phase are based on a traffic light system:

Go

80-100% recruitment achieved. Progress to main trials following a review of screening logs and protocol. Any barriers for recruitment will be addressed.

Amend

30-79% recruitment achieved. Potentially progress to main trial with additional sites being recruited as well as a screening log and protocol review, following discussion with Trial Steering Committee and HTA.

Stop

Less than 30% recruitment achieved. The decision to progress will be made by the Trial Steering Committee in association with the HTA s.

Protocol compliance and the completeness of follow-up data will also be reviewed by the TSC and DMC, noting that primary outcome data will not be available for patients at the end of the pilot.

If the loss to follow-up (for those who have observed >3 months follow-up) exceeds

20% without an identifiable and correctable reason it would not be feasible to progress to the main trial without substantial changes in the study design.

15.3 Number of Participants to be enrolled

POLYFIX DCM plans to include 394 participants in total. The pilot phase aims to assess at least 40 participants.

The minimum clinically important difference (MCID) for the mJOA is estimated to be between 1 and 2 points[86]. As the mJOA is demonstrated to improve greater than the MCID with surgery (including laminectomy or laminectomy with fusion) alone [11,13], with the amount of change linked to the pre-operative baseline[13]. Consequently, in consensus with patients, we have determined a MCID for the mJOA of 1 point for additional gains. This is in keeping with the trial design of recent DCM RCTs, CSM Protect NCT01257828[89] and RECEDE-Myelopathy (EduraCT number: 2017-004856-41). This has been modelled to ensure statistical power across all baseline scenarios.

On this basis, a total sample size of 394 participants under equal randomisation will provide 90% power (accounting for 10% drop out rate) to detect a change of 1 from baseline on the mJOA scale (assuming a standard deviation [SD] of 2.89), using a two-sided t-test at a 5% significance level.

15.4 Criteria for the premature termination of the trial

Aside from the recruitment parameter defined above for the internal pilot, there are no defined criteria for the premature discontinuation of the trial. However, the IDMC and TSC will make recommendations on the discontinuation of the trial following review of the on-going patient safety and efficacy data presented at regular scheduled meetings.

15.5 Procedure to account for missing or spurious data

The data will be analysed in two populations, a safety population that includes all patients who have consented to the trial, and a full analysis population that include all patients who are randomised. Groups will be allocated using the ITT principle that looks at which arm they were randomised to, disregarding subsequent deviations from protocol.

15.6 Economic evaluation

Initially a within trial economic analysis will be conducted as it is envisaged that the majority of any difference in costs and/or benefits will present within the trial follow-up period. In terms of costs we will focus on large cost drivers and those resources that are expected to differ between arms. Resource items to be measured will thereby include those associated with the additional surgical intervention (including operation time), length of stay, any re-admissions, visits to particular health professionals e.g. GP, and certain medications. This will enable costs to be estimated from the viewpoint of the NHS and personal social services (PSS). Additionally, other societal costs e.g. if/when participants return to work will also be considered. As such, participants will be asked to complete a self-report resource use/employment questionnaire at baseline, 6,12 and 24 months post-randomisation. The main measure of outcome in the economic analysis will be the EQ-5D (50) as this can be used to generate Quality Adjusted Life Years.

Responses to the EQ-5D will be requested via a self-report questionnaire and collection of carer quality of life in a similar way will also be considered.

The above analyses will enable both the estimated incremental cost and incremental effect associated with laminectomy to be compared to laminectomy and fusion. Assuming dominance does not occur (where one option is estimated to be more effective and less costly than the other option), the incremental cost-effectiveness ratio of the more costly option will then be estimated and assessed in relation to a range of cost-effectiveness thresholds e.g. £20,000-£30,000 per QALY is recommended by NICE. The associated level of uncertainty will also be characterised by estimating cost-effectiveness acceptability curves. A sensitivity analysis will be undertaken to assess the robustness of conclusions to changes in key assumptions.

Additionally, if there is a difference in outcome at the 24-months follow up point, then there would be the potential for benefits to accrue over a number of years. Therefore, the within-trial cost-effectiveness evaluation will be supplemented with probabilistic long run economic model comprising two parts. Firstly, we will construct a decision tree to use the results of the trial to assign individuals to various relevant health states. A long run Markov model will then estimate costs and benefits (QALY) over the expected lifetime of participants. The structure of these models will be developed in consultation with clinical experts. Data to inform the model will be taken from the trial, and where necessary, from the literature or from expert opinion. As this is a novel trial there may be limited data on the confidence of any persistence of differences seen. A modelling approach will therefore also enable the exploration of the effect of different assumptions relating to long term effects.

Subject to additional funding to enable access, data obtained through linkage (e.g. Hospital Episode Statistics) will also be used to inform these calculations.

15.7 Definition of the end of the trial

The end of the trial will be 24 months post-surgery for the last patient recruited.

16 Data handling and record keeping

16.1 CRF

Electronic case report forms will be used to collect the data, with paper forms as back up. All data will be entered onto a secure electronic database. The database, which will be and GDPR compliant, will be secured by appropriate access control and password protection. All trial data in the CRF must be extracted from and be consistent with the relevant source documents. The CRFs must be completed by the investigator or designee in a timely manner. It remains the responsibility of the investigator for the timing, completeness and accuracy of the CRF pages. The CRF will be accessible to trial coordinators, data managers, the investigators, Clinical Trial Monitors, Auditors and Inspectors as required.

Data provided to the central coordinating team will be checked for errors, inconsistencies and omissions. If missing or questionable data are identified, the central coordinating team will request that the data be clarified.

Study participants will provide explicit consent to the use of identifiable data for the purposes of the conduct of the study (e.g. centralised follow-up). The POLYFIX DCM trial management team will hold patient identifiable data (PID) on all participants including name, date of birth, gender,

NHS number or equivalent, home address and postcode, telephone number and email address where applicable.

For the purposes of data analysis the patient identifying information will be replaced with unique patient specific trials study code to anonymise the data and also allow for central blinded follow up. Sites will keep all data collected from their patients with personal data (e.g. full name, DoB, address etc) as well as completed/signed consent forms in their Site Files. When they enter data collected on the CRF to send to us each patient will only be identified by their trial ID number and their DoB.

To comply with data protection legislation, PID will not be transferred to the UK from international sites. For international sites, their centralised follow up will be coordinated by a single lead centre.

PID will be accessible to a limited members of the trial team within the Cambridge Clinical Trials Unit, sponsor monitors auditors and inspectors as required. This is necessary to 1) perform any linkage to national datasets (NHS Digital, Secure Anonymised Information Linkage, Public Health Wales, electronic Data Research and Innovation Service, Public Health Scotland and Belfast Health and Social Care Trust, and 2) to contact participants for follow-up assessments and is therefore imperative to the conduct of the study.

All PID downloaded from NHS Digital and the equivalent national health record organisations will be stored securely on the University of Cambridge, School of Clinical Medicine Secure Data Hosting Service (SDHS). The SDHS is registered and approved under the NHS Digital Data Security and Protection Toolkit and is ISO 27001 certified.

16.2 Source Data

To enable peer review, monitoring, audit and/or inspection the investigator must agree to keep records of all participating participants (sufficient information to link records e.g., CRFs, hospital records and samples), all original signed in formed consent forms. The electronic CRFs should also be readily available. Data records will be kept for 10 years after the study.

In this trial the following documentation will be considered as source data:

- Patient medical notes, electronic and/or paper as applicable
- Screening Logs
- Informed Consent Forms
- Questionnaires

16.3 Data Protection & Participant Confidentiality

All investigators and trial site staff involved in this trial must comply with the requirements of the Data Protection Act 2018 and Trust Policy with regards to the collection, storage, processing, transfer and disclosure of personal information and will uphold the Act's core principles.

17 Data Monitoring Committee/Trial Steering Committee

The Trial Steering Committee (TSC) will provide overall supervision with respect to the conduct of the trial. The TSC will consist of an independent Chairperson, the Chief Investigator and additional relevant but independent stakeholders. Principal Investigators from each participating site and members of the Trial Management Group (e.g. trial statistician, trial manager, data manager) will be invited to meeting as

observers. A representative of the Funder and Sponsor will also be invited to the TSC meetings. The TSC will meet once a year (or more frequently if required) to review trial progress. Full details of the TSC membership and remit can be found in the TSC Charter.

The ethical and safety aspects of the trial will be overseen by an independent Data Monitoring Committee (IDMC) who will meet once a year and their meetings will be timed so that reports can be fed into the TSC meetings. Dr Michael Fehlings, Professor of Neurosurgery, University of Toronto who has been involved numerous trials within DCM, including the only two previous RCTs will chair the IDMC Full details of the IDMC membership and remit can be found in the IDMC Charter.

A summary figure, representing the working interaction of these committees is in Figure 1.

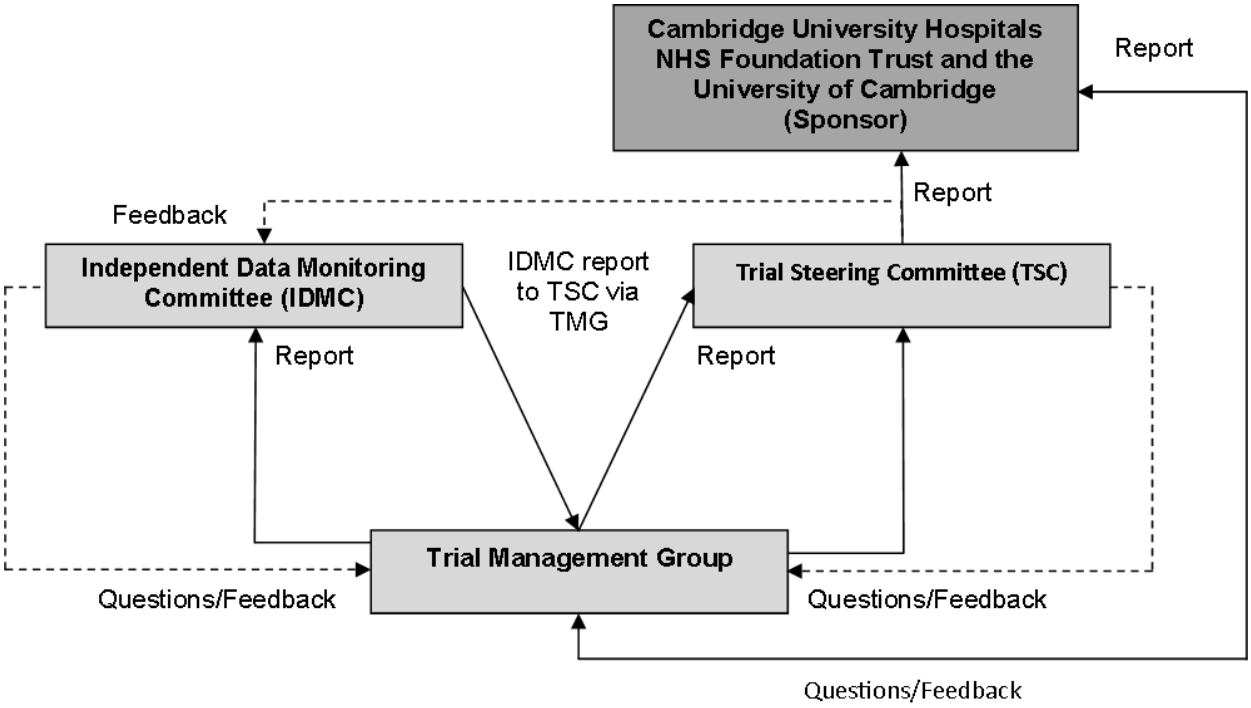


Figure 1: Diagram of Relationships between Trial Committees and Group

18 Ethical & Regulatory considerations

18.1 Ethical committee review

Before the start of the trial or implementation of any amendment we will obtain approval of the trial protocol, protocol amendments, informed consent forms and other relevant documents e.g.advertisements and GP information letters if applicable, from the REC. All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

Annual reports will be submitted to the REC in accordance with national requirements. It is the Chief Investigator's responsibility to produce the annual reports as required.

18.2 Protocol Amendments

Protocol amendments must be reviewed and agreement received from the Sponsor for all proposed amendments prior to submission to the REC/ HRA.

The only circumstance in which an amendment may be initiated prior to REC/HRA, approval is where the change is necessary to eliminate apparent, immediate risks to the participants (Urgent Safety Measures). In this case, accrual of new participants will be halted until the HRA, REC approval has been obtained.

The CI is delegated the responsibility to take appropriate Urgent Safety Measures. The CI must notify the, REC and Sponsor immediately and in any event no later than 3 days from the date the measures are taken. In addition, the CI should inform all participating sites and Principal Investigators of the Implementation of Urgent Safety Measures immediately or within a maximum of three days in writing by email.

18.3 Peer Review

In addition to the extensive trial collaborators listed in the initial pages of this document, this trial has been peer reviewed by the NIHR HTA as part of the funding award process.

18.4 Declaration of Helsinki and Good Clinical Practice

The trial will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the conditions and principles of Good Clinical Practice, the protocol and applicable local regulatory requirements and laws.

18.5 GCP Training

All trial staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. This training should be updated every 2 years or in accordance with your Trust's policy.

19 Sponsorship, Financial and Insurance

The trial is sponsored by Cambridge University Hospitals NHS Foundation Trust and University of Cambridge.

This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) (NIHR131243). This does not include the provision of MoveMed, which is provided by MoveMed Ltd acting as a project collaborator. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should

a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

A contribution towards participants' travelling expenses will be made.

20 Monitoring, Audit & Inspection

Should a monitoring visit or audit be requested, the investigator must make the trial documentation and source data available to the Sponsor's representative. All participant data must be handled and treated confidentially.

The Sponsor's monitoring frequency will be determined by an initial risk assessment performed prior to the start of the trial. A detailed monitoring plan will be generated detailing the frequency and scope of the monitoring for the trial. Throughout the course of the trial, the risk assessment will be reviewed, and the monitoring frequency adjusted as necessary.

Remote monitoring will be conducted for all participating sites. The scope and frequency of the monitoring will be determined by the risk assessment and detailed in the Monitoring Plan for the trial.

21 Protocol Compliance and Breaches of GCP

Prospective, planned deviations or waivers to the protocol are not and must not be used.

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. They can happen at any time but are not planned. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

Deviations from the protocol which are found to occur constantly again and again will not be accepted and will require immediate action and could potentially be classified as a serious breach.

Any potential/suspected serious breaches of GCP must be reported immediately to the Sponsor without any delay.

22 Publications policy

Ownership of the data arising from this trial resides with the trial team. On completion of the trial the data will be analysed and tabulated and a Final Trial Report prepared.

We intend to disseminate the findings via peer-reviewed journals and presentations at national and international meetings. In addition to meetings orientated around neurosurgery, we will target conferences organised for the different health professionals who care for patients with DCM, including Neurology, Primary Care, Geriatrics and Rehabilitation medicine. We will publish the results of the trial on the EudraCT website.

Research findings will be disseminated to relevant service user groups and charities (including Myelopathy.org) through newsletters, website posts and public presentations. The dedicated trial website will also include dedicated pages for members of the public. We will present the trial in open days organised by hospitals participating in the trial where members of the public are invited to find out about on-going research.

Participants will be able to view global trial results on the trial website.
The trial partners, funders and sponsor will be acknowledged in the publication. Any scientific paper, presentation or communication concerning the trial shall be submitted to each relevant party following their guidelines. The trial protocol will be published in advance, and registered with a trial database

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24 Appendices

24.1 Appendix 1 - Trial Management / Responsibilities

24.1.1 Participant registration/ Randomisation procedure

Sealed envelope (an external supplier of a web-based randomisation system that meets the requirements of FDA and EMA) will be used for participant randomisation (https://www.sealedenvelope.com) and this will be provided and supported by the Cambridge Clinical Trials Unit. The randomisation of participants will be undertaken by the trial team at each participating site following confirmation of eligibility.

24.1.2 CRF Completion & Data management

Data collection and CRF completion will be undertaken by delegated research staff at each participating site within agreed timelines (detailed CRF completion guidelines will be provided to participating sites) Data management will be undertaken by the Cambridge Clinical Trials Unit and all data management activities will be described in the trial specific Data Management Plan.

24.1.3 Preparation and submission of Annual Progress and Safety Reports

The preparation and submission of amendments and all annual progress and safety reports will be undertaken by the Chief Investigator/trial team in collaboration with the CCTU.

24.1.4 Preparation and submission of amendments

Amendments to the trial will be prepared and submitted to the appropriate authorities by CCTU. Approvals will then be disseminated to all sites prior to implementation.

24.1.5 Data protection/confidentiality

All identifiable data will be securely sent to the coordination centre (CCTU) via NHS secure email (i.e. from @nhs.net account to [trial specific email address@nhs.net) and stored in a separate password-protected database in compliance with the GDPR and the Data Protection Act 2018, with permission for access restricted to delegated trial staff. Consent will be sought for the transfer or identifiable information.

24.1.6 Trial documentation and archiving

All trial documentation will be stored in a secure location during the conduct of the trial . Each participating site will be responsible for archiving their own trial data including source data, CRFs and the Investigator Site File (ISF) for the appropriate time period as determined by the relevant regulations at the time of archiving. The archiving facility may be at the participating site or at another appropriate location off-site as per local policy. The Chief Investigator will advise when the site can arrange archiving and the site will need to provide details of the archiving facility used. In case of audit or inspection following archiving of trial documentation, the site will be expected to retrieve the relevant documentation within a reasonable timeframe.

24.2 Appendix 2 – Authorisation of Participating Sites

24.2.1 Required Documentation

Prior to initiating a participating site the following documentation is required:

- Completed delegation log
- CVs and GCP certificates of PI and key members of staff listed on delegation log
- Capacity and Capability from site R&D
- Fully executed Participant Site Agreement
- Participant Information sheets and other leaflets printed on site letterhead
- Protocol signed and dated by PI

24.2.2 Procedure for initiating/opening a new site

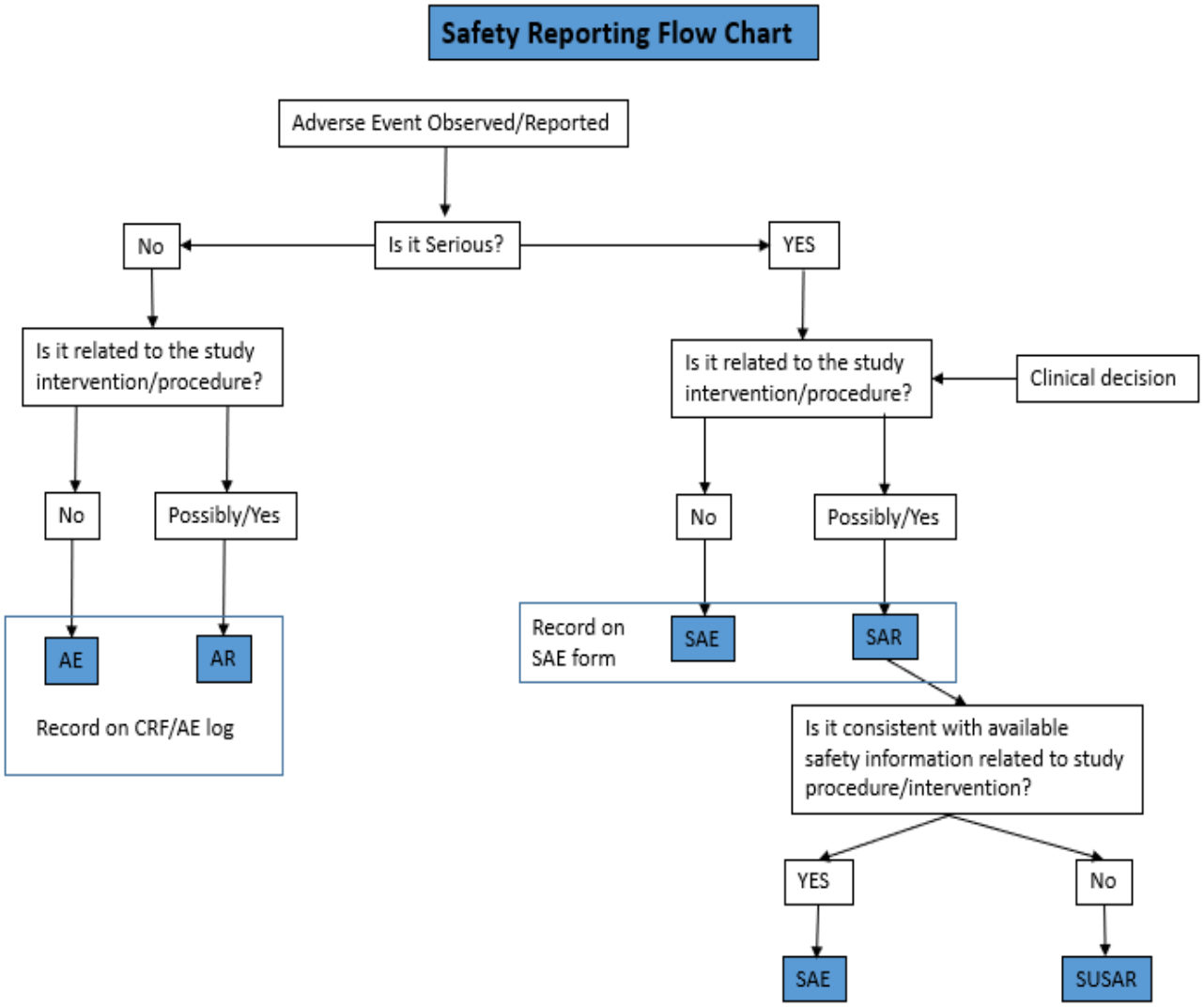
Following all required approvals from REC/HRA and once all required documents have been received from the participating site, the trial coordinator will arrange for a Site Initiation Visit (SIV) which will take place either in person or via teleconference. The purpose of the SIV is to explain in detail and provide training to the trial procedures to the site staff. The SIV will be arranged and chaired by the trial coordinator. A trial initiation form will be completed during the meeting and everybody present will be required to sign a training log. Following this meeting and once any outstanding issues have been resolved the trial coordinator will email the site to confirm that they can open to recruitment. Copies of the SIV documentation will be filed in the TMF and ISF as appropriate.

24.2.3 Principal Investigator Responsibilities

The Principal Investigator (PI) has overall responsibility for the conduct of the clinical trial at his/her participating site. The PI's responsibilities include (but are not limited to):

- Attendance at the site initiation meeting
- Continuous oversight of the conduct of the trial at the site
- Ensuring that all required local approvals for the conduct of the trial at the site are in place before participant recruitment commences
- Ensuring that the trial is conducted according to the protocol and the principles of Good Clinical Practice (GCP)
- Maintaining the Investigator Site File and ensuring that it is kept up to date.
- Delegation of responsibilities to appropriately trained staff (this must be documented on the delegation of responsibility log)
- Providing protocol or specialized training to all members of the local trial team (including new members joining during the course of the trial) and ensuring that tasks are delegated to members of staff who have the appropriate training and qualifications
- Accurate collection of participant data and entering into CRFs within agreed timelines and timely resolution of data queries.
- Safety reporting to Sponsor within the required timelines
- Dissemination of important safety and other trial related information to all stakeholders at the participating site

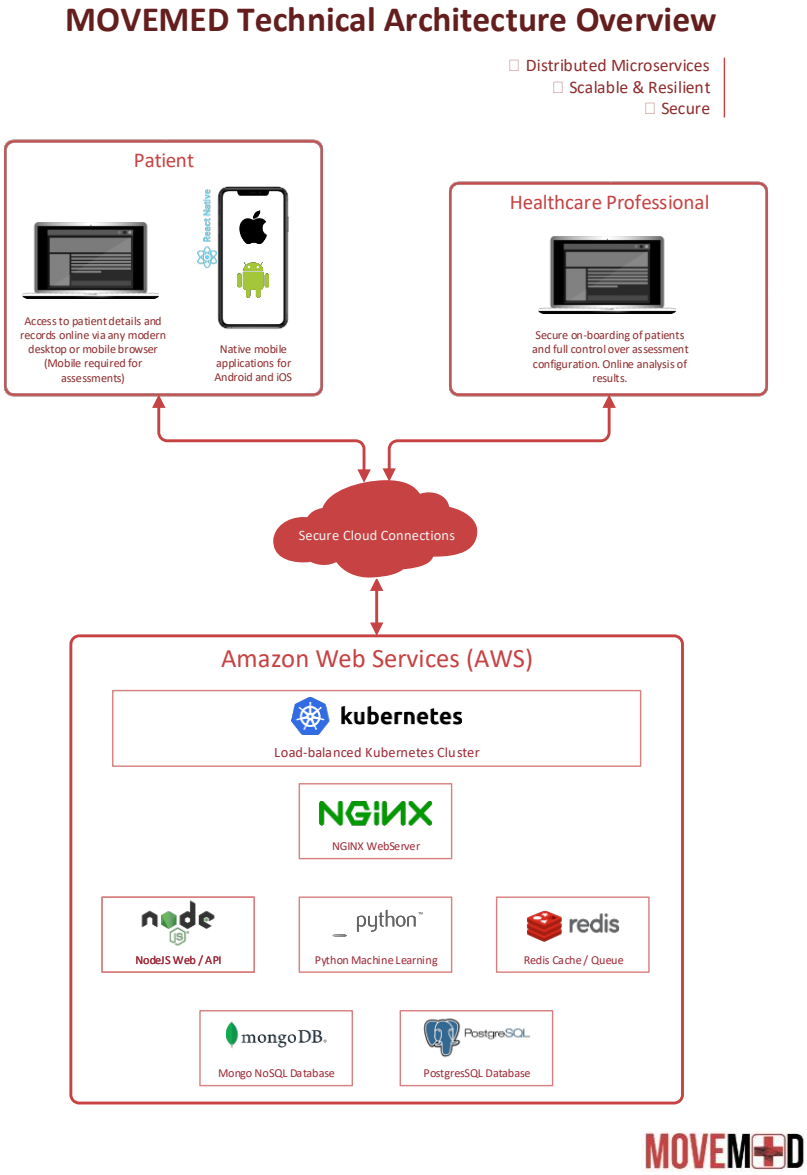
24.3 Appendix 3 – Safety Reporting Flow Chart



24.4 Appendix 4 – MoveMed

Overview of MoveMed

MoveMed (MoveMed, Cambridge, UK) uses an application on the patient's smartphone (Android or iOS operating systems) to assess DCM. Data is held securely (Amazon Web Services, Washington USA) using two factor authentication and double encryption, with partitioning of personal identifiers from outcome data. Data is analysed within the cloud and can be displayed using web-based portals. The portal enables a clinician to view their patients' performance remotely, and over time. (Figure 2) MoveMed is compliant pre-regulatory approvals (e.g. CE / CA Mark).



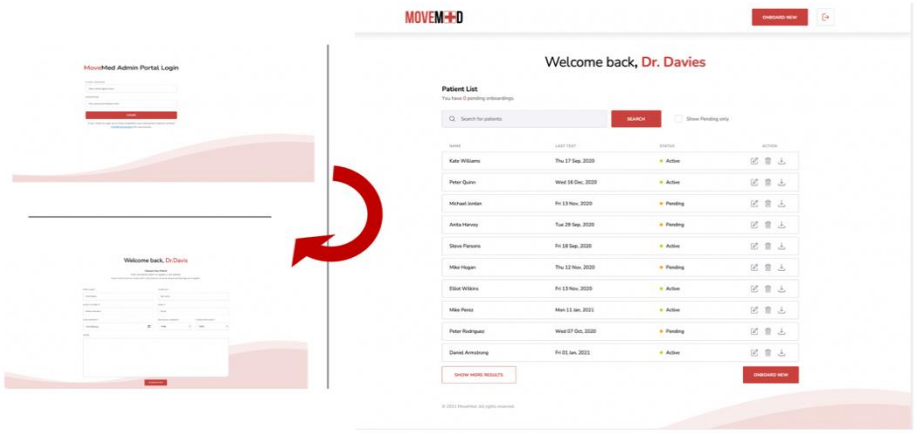


Figure 2. Overview of MoveMed

The smartphone application is made up of 'interactive' assessment and 'passive' assessments. Interactive assessments require the patient to complete a specific task. There are 5 in total (Figure 3), including 3 on-screen tasks (e.g. typing, or interacting with targets) and 2 off-screen tasks (e.g. holding the phone steady, or walking with it). By recording the screen interactions (time and location) and/or accelerometer/gyroscope data (time, x-y-z coordinates), we have developed new digital metrics of dexterity and gait, such as *touch accuracy*, *finger speed*, *typing error frequency*, *postural drift*, *stride length variability*. These active assessments take ~10 minutes to complete. The user can complete them as frequently as desired but will be prompted to complete them every three days. Video instructions for the tests can be find at this link: https://movemed.io/walkthroughs

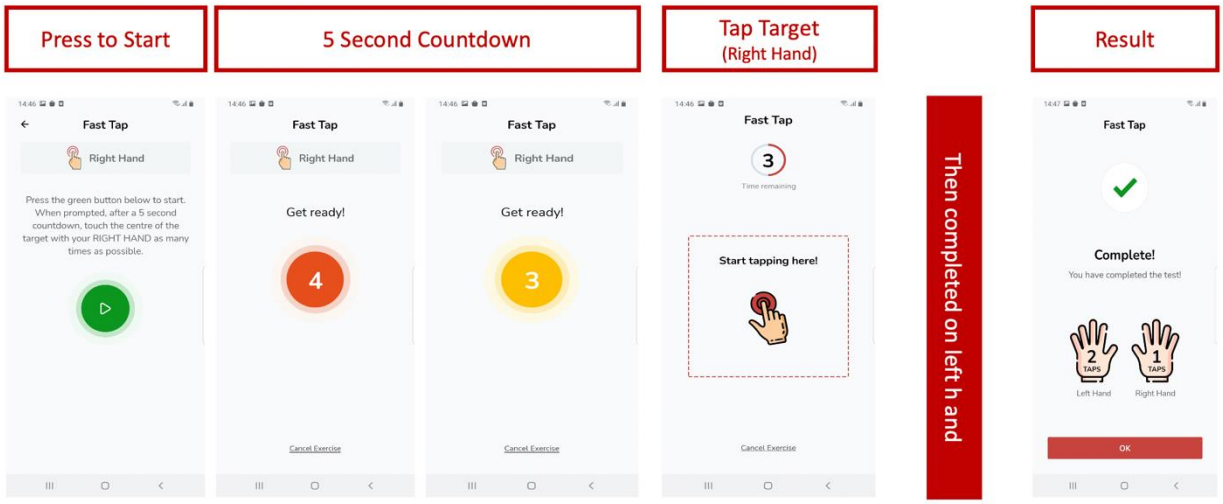


Figure 3: Two DCM assessments from the MoveMed Application. 'Tap' before (Screen 1) and during (Screen 2), and 'Type' (Screen 3)

Additionally, keyboard interactions and activity data from accelerometer / gyrometer are monitored in the background. The patient journey is displayed in Figure 4.

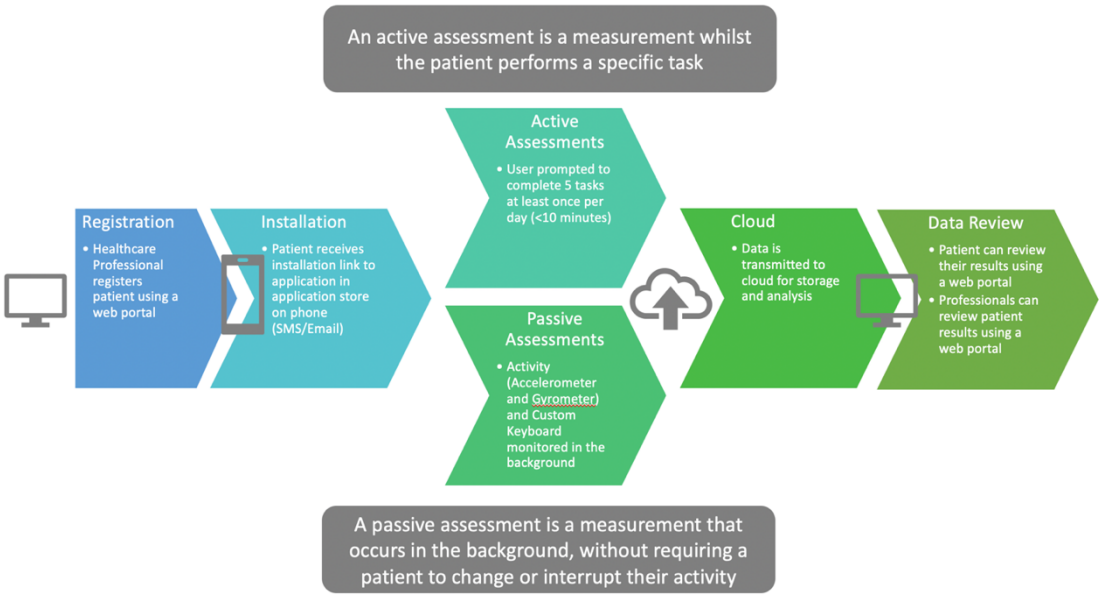


Figure 4. Patient Journey in MoveMed

Eligibility for MoveMed

MoveMed uses an application on the patient's smartphone to assess DCM, and therefore requires a compatible smartphone. Using an analysis of 16,000 visits to Myelopathy.org, a DCM charity, 50% of access was via a compatible smartphone, equally by men and women and prevalent amongst older age groups[76].