JRMO Research Protocol for Interventional Studies

Full Title	**Artificial intelligence-assisted magnetic resonance imaging for quality, efficiency and equity in the NHS care of multiple sclerosis**
Short Title	AssistMS
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Edge Number	173986
REC Reference	24/PR/1584
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Summary of Changes

Version Number	Version Date	Amendment Number	Summary of Changes
V1.0	30Oct2024	N/A	N/A - 1st version
V2.0	20Mar2025	AM01 (NSA01)	Table 1, section 9.3.1 and 11.2.3: changes to the randomisation procedure. Section 9.2: minor changes to the CONSORT reporting
V3.0	24Nov2025	AM03 (NSA03)	Addition of 3 participating sites to the list of sites on page 2. Update to the Principal Investigator at Barts Health in accordance with the original IRAS.

1. Contents

2. Glossary

9HPT	Nine-hole peg test
AE	Adverse Event
AI	Artificial Intelligence
AMA	American Medical Association
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CAG	Confidentiality Advisory Group
CAPA	Corrective And Preventive Actions
CE	Conformité Européenne
CI	Chief Investigator
CIS	Clinically Isolated Syndrome
CPT	Current Procedural Terminology
CRA	Clinical Research Associate
(e)CRF	(electronic) Case Report Form
CRO	Contract Research Organisation
CSF	Cerebro-spinal fluid
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTN	Clinical Trials Network
DMC	Data Monitoring Committee

DMT	Disease modifying treatment
DOB	Date of Birth
EC	European Commission
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EMR	Electronic Medical Records
EoT	End of Trial
EQ-5D-5L	Euro Quality of Life Dimensions 5 Levels
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EudraVIGILANCE	European Union Drug Regulating Authorities Pharmacovigilance
FLAIR	Fluid-attenuated Inversion Recovery
FOV	Field Of View
FPFV	First Patient First Visit
FSN	Field Safety Notice
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
Gd+ lesion	Gadolinium positive lesion
Gd- lesion	Gadolinium negative lesion
HCP	Health Care Professional
HE	Health Economics

HIPAA	Health Insurance Portability and Accountability
HRA	Health Reimbursement Arrangements
IC	Informed Consent
ICER	Incremental Cost Effectiveness Ratio
ID	Identification
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IPR	Intellectual Property Rights
IRB	Investigational Review Board
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IT	Information Technology
ITT	Intention To Treat
JRMO	Joint Research Management Office
LPLV	Last Patient Last Visit
LST	Lesion Segmentation Toolbox
M12	Month 12
MA	Marketing Authorisation
Main REC	Main Research Ethics Committee
MDD	Medical Device Directive
MDT	Multidisciplinary Team Meeting
MDR	Medical Device Regulation

MHRA	Medicines and Healthcare Products Regulatory Agency
MIB	Medtech Innovation Briefing
MIR	Manufacturer Incidence Report
MoA	Mechanism of Action
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
NPT	Non-Pharmaceutical Treatment
PACS	Picture Archiving and Communication Systems
PBVC	Percentage Brain Volume Change
PDDS	Patient Determined Disease Steps
PI	Principal Investigator
PIS	Participant Information Sheet
PMS	Progressive Multiple Sclerosis
PPMS	Primary Progressive MS
PPI	Patient and Public Involvement
PRO	Patient Reported Outcome
pwMS	Person with Multiple Sclerosis
pwRMS	Person with early/relapsing Multiple Sclerosis
QA	Quality Assurance

QALY	Quality Adjusted Life Year
QC	Quality Control
QMUL	Queen Mary University of London
QOL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
RRMS	Relapsing-remitting Multiple Sclerosis
Sa	Statistical accuracy
SC	Spinal cord
SaaS	Software as a Service
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SDV	Source Document Verification
SIENA	Structural Image Evaluation using Normalisation of Atrophy
SmPC	Summary of Product Characteristics
s-Nfl	Serum neuro-filament light chain
SoC	Standard of Care
SOP	Standard Operating Procedure

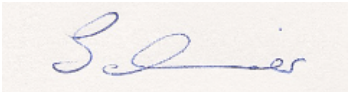
Sp	Statistical precision
SPMS	Secondary Progressive Multiple Sclerosis
SSA	Site Specific Assessment
SST	Symbol Substitution Task
SUS	System Usability Scale
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Tesla
TMC	Trial Management Committee
TMG	Trial Management Group
TMF	Trial Master File
TLS	Transport Layer Security
TOM	Technical and Organisational Measures
TSC	Trial Steering Committee
T25-FW	Timed 25-foot Walk test
UK	United Kingdom
US	United States
UAT	User Acceptance Test
WBV	Whole Brain Volume

3. Signature page

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice (GCP), the United Kingdom (UK) Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: **Prof Klaus Schmierer**

Signature: 

Date: **20 Mar 2025**

Statistician's Agreement

The study as detailed within this research protocol will be conducted in accordance with the current UK Policy Framework for Health and Social Care Research, the World Medical Association Declaration of Helsinki (1996), principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.

I take responsibility for ensuring the statistical work in this protocol is accurate, and I take responsibility for statistical analysis and oversight in this study.

Statistician's name: **__Nicholas Magill__**

Signature: 

Date: **___06/12/2024____**

4. Summary and synopsis

Table 1: Summary and synopsis

Full title	Artificial intelligence-assisted magnetic resonance imaging for quality, efficiency and equity in the NHS care of multiple sclerosis - phase III: real world testing of ico**brain ms**
Short title	AssistMS
Sponsor	Queen Mary University of London (QMUL)
Methodology	Prospective individual randomised controlled trial
Research setting	UK only, multi-centre (<5 sites), NHS sites only
Objectives / aims	To assess the clinical usefulness and cost-effectiveness of an Artificial Intelligence (AI) brain magnetic resonance imaging (MRI) quantification tool called ico**brain ms**, and to test its implementation in routine care at three clinical research sites.
Number of participants	1336
Inclusion and exclusion criteria	Inclusion criteria are: - 18 years of age and above - Clinically Isolated Syndrome suggestive of demyelination (CIS) or definitive diagnosis of MS - Undergoing MRI head investigation - On an MS DMT pathway - Access to a smartphone, tablet or computer Exclusion criteria is: - People with MS (pwMS) participating in a randomised controlled Clinical Trial of an investigational medicinal product (CTIMP) (pwMS participating in a single arm study may be included, provided this is acceptable with the CTIMP protocol)

Table 1: Summary and synopsis (continued)

Statistical methodology and analysis (if applicable)	The clinical usefulness of ico**brain ms** will be assessed by evaluating its impact on the detection of disease activity on assessment of MRI by a (neuro)radiologist. Disease activity will be defined as the presence of new and/or expanding lesions. Radiological assessments of disease activity will be available for all participants at year 1, using comparison to the baseline MRI scan. Some participants are anticipated who will also have radiological assessment available at baseline, by making use of a retrospective MRI scan (i.e. MRI done at a visit prior to the trial). The primary analysis will be a comparison of the odds of disease activity being detected on radiological assessment between the ico**brain ms** and standard of care arms (SoC). This comparison will be done using a logistic generalised estimated equations (GEE) model with robust standard errors to account for repeated MRI scans on the same participant and adjusting for the randomisation stratification variables. SoC arm: Radiological reading by a neuro-radiologist Interventional arm: Radiological reading by a neuro-radiologist assisted by ico**brain ms**. The primary analysis will be conducted on an intention to treat (ITT) basis.
Device Classification (for icobrain MS)	**Class IIa** (classification is based on the medical device risk level to the end user, as set out in Annex VIII of the EU MDR 2017/745). ico**brain** is classified as a class B (Non-serious Injury is possible) per IEC 62304. No serious injury is possible with the use of ico**brain**. The software is intended to assist Health Care Professionals (HCP) by providing quantitative measurements of segmentable brain structures. These measurements are presented to a HCP in a report to improve monitoring.
Medical condition or disease under investigation	Multiple Sclerosis (MS)
Investigational Device	ico**brain ms**
Treatment duration	Not applicable. Intervention is a non-invasive medical device (AI-assistive software)
Follow up duration	N/A
Total duration for participants	12 months and up to 12 weeks (MRI reporting variability)

Table 1: Summary and synopsis (continued)

Planned enrolment period	12 months
Planned duration of investigation	27-30 months (1st site opening to LPLV)
End of trial definition	End of Trial (EoT) is defined as the date of Last Participant Last Visit MDT (LPLV MDT). Due to the nature of the trial, this will either be when the LPLV is at their final M12 MRI or their M12 clinical visit, whichever event occurs last. However, as any patient discussion and treatment decisions will be decided at their MDT and need to capture this data, this is the End of Trial.

5.Introduction

5.1 Background

Multiple Sclerosis (MS) is a common neurological disorder in the United Kingdom (UK) affecting over 150,000 individuals ("MS in the UK," n.d.). Without adequate disease modifying treatment (DMT), the majority of people with MS (pwMS) will develop significant disability within 10 years of onset (Confavreux and Vukusic 2006). The resulting annual cost of MS in the UK is about £1 billion, the largest proportion of which is allocated to people with significant disability (McCrone et al. 2008; Thompson et al. 2018) . The main challenge in treating MS is to provide patients with a DMT that is able to reduce disease activity in order to prevent brain damage and progression of neurological disability (Giovannoni et al. 2016a).

A typical MS disease course involves relapses (acute attack of symptoms), followed by progressive disease. About 80–90% of people with MS will initially have the relapsing form of the disease (RMS) which can further develop in a progressive stage of the disease, known as Secondary Progressive Multiple Sclerosis (SPMS). In addition, about 10–15% of people with MS have a progressive disease course from the outset, with gradual progression of clinical symptoms in the absence of relapses; this is known as Primary Progressive MS (PPMS). A number of DMTs have been approved for treating MS. These drugs can directly affect the disease course by reducing relapses, slowing disability progression, reducing the number of new lesions and slowing the brain atrophy rate. They are not all equally effective in all pwMS, have different modes of action, and variable side-effect profiles. Since there are no clinical features or biomarkers enabling prediction of the success or failure of a specific DMT in the individual pwMS, timely detection of treatment failure is key to ensure that patients receive the most adequate treatment to preserve neurological function (Hobart et al. 2019).

Most of the pathological events in the brain of pwMS are clinically silent, and MRI has become the most useful tool to detect such subclinical disease activity in order to evaluate treatment response and inform clinical decisions (Montalban et al. 2018). In

this context, disease activity and treatment response are typically evaluated by longitudinal changes on the brain MRI scans looking at new/enlarging lesions and/or brain atrophy (Montalban et al. 2018; Sastre-Garriga et al. 2020).
Current evaluation of brain MRI scans in a clinical setting requires visual inspection, of which sensitivity is degraded by multiple human, technical, and technological factors, including lack of time and fatigue of (neuro)radiologists, limited expertise and sub-specialisation, and lack of standardisation of image acquisition protocols across the National Health Service (NHS) ("Clinical radiology UK workforce census 2020 report" 2020; Dahan, Wang, and Gaillard 2018; Schmierer et al. 2019; W. Wang et al. 2017). These factors make it difficult for radiologists to detect small lesions, and virtually impossible to measure brain volumes and - therefore - to calculate brain atrophy. Indeed, today's radiological reports contain errors in almost 1/4 cases, are subject to significant inter-rater variability, and can miss subtle, but clinically relevant, findings. As a consequence, 26% - 40% of pwMS are estimated to be on a suboptimal DMT for an average of 3.9 years (Daugherty et al. 2005; Río et al. 2012; Sá, de Sá, and Sousa 2014a).

MRI-readings can be significantly enhanced by AI-assistive software. Evidence suggests the rate of new lesion detection to be 3 - 4 times higher when using assistive software compared to visual inspection of MRI scans (Dahan, Wang, and Gaillard 2018; W. Wang et al. 2017; Pregliasco et al. 2018; Van Heerden et al. 2015; Zopfs et al. 2019). ico**brain ms** (ico**metrix**) is an AI-assistive software which quantifies brain MRIs and summarises clinically relevant findings (white matter lesions and brain atrophy) for pwMS in structured electronic radiological reports and annotated images. Complementing the radiologist's visual assessment, ico**brain ms** improves the sensitivity to detect disease activity that may indicate a suboptimal response to DMT in patients with RRMS, which ultimately may contribute to clinical decision-making on starting treatment or switching to an alternative agent.

ico**brain ms** has been extensively validated regarding technical performance and clinical relevance in multiple studies (H. N. Beadnall et al. 2019a; Jain et al. 2015b; D. Smeets et al. 2016; Rakić, Vercruyssen, Van Eyndhoven, la Rosa, et al. 2021; D. M. Sima, Billiet, Vyvere, Maertens, et al. 2017; A. Tsang et al. 2018; C. Wang et al. 2016a; Finkelsztejn, Dadalti Fragoso, et al. 2018; Lysandropoulos et al. 2016a; Akaishi et al. 2020a; D'hooghe, Gielen, Van Remoortel, D'haeseleer, Peeters, Cambron, Keyser, et al. 2019; Fragoso, Wille, Abreu, Brooks, Dias, Duarte, Farage, Finkelsztejn, Frohlich, Goncalves, Guedes, Medeiros, Oliveira, Ribas, da Rocha, Santos, Scorcine, da Silveira, Spedo, Tauil, Varela, and Vieira 2017; Golan et al. 2020a; D. Horakova et al. 2020). Furthermore, the comparative clinical usefulness of ico**brain ms** has been evaluated in some initial studies (D. Sima et al. 2018; Diana M. Sima et al. 2020; in Van Hecke et al. 2021a) (Van Hecke et al. 2019; H. Beadnall et al. 2017; H. N. Beadnall et al. 2018) and an early economic evaluation has been performed ({Esposito, Sima, and } 2021). Overall, ico**brain ms** has been recognised as the best validated brain MRI volumetric tool in the field of MS (Mendelsohn et al. 2023), demonstrating accurate, reproducible and reliable quantification of both lesion and brain volumes.

In July of 2023, ico**metrix** was granted a Current Procedural Terminology (CPT) code from the American Medical Association (AMA) that is effective as of January 1st 2024, thereby supporting reimbursement of the ico**brain** tools in clinical practice in the United States (US). This is a significant indication that ico**brain ms** will be used for routine clinical care in the US as a part of precision and personalised medicine ("AMA Issues CPT Code for AI-Related Brain MRI Quantification," n.d.). Moreover, particularly relevant for this study, the National Institute for Health and Care Excellence (NICE) developed a medtech innovation briefing in 2022 highlighting that there is evidence for system benefits because of reductions in staff time and, although more research is warranted, potentially also patient benefits.

Although current research has provided evidence suggesting that ico**brain ms** could aid decision making and bring benefits to healthcare (Van Hecke et al. 2019, 2021a; H. N. Beadnall et al. 2018; {Esposito, Sima, and } 2021; Diana M. Sima et al. 2021), the precise impact of ico**brain ms** in NHS practice remains uncertain and requires thorough evaluation.

Therefore, the main aims of this study are:

1. To assess the clinical usefulness of ico**brain ms** by evaluating the superiority of ico**brain ms**, in combination with radiological reading by a neuro-radiologist, in detecting disease-activity over Standard of Care (SoC) (radiological reading by a neuro-radiologist only) in a real world NHS setting.
2. To undertake a health-economic assessment of the impact of ico**brain ms** on disease management, decision-making, health and social care resource use, and quality of life

5.2 Preclinical data

Several peer-reviewed publications (H. N. Beadnall et al. 2019a; Jain et al. 2015b; D. Smeets et al. 2016; Rakić, Vercruyssen, Van Eyndhoven, la Rosa, et al. 2021; D. M. Sima, Billiet, Vyvere, Maertens, et al. 2017; A. Tsang et al. 2018; C. Wang et al. 2016a; Finkelsztejn, Dadalti Fragoso, et al. 2018; Lysandropoulos et al. 2016a; Akaishi et al. 2020a) and regulatory filings (FDA/CE/MDSAP) presented ico**brain ms** technical performance using relevant datasets. Furthermore**,** ico**brain ms** was also used in some studies investigating the correlation between MRI biomarkers and clinical outcomes (Akaishi et al. 2020a; D'hooghe, Gielen, Van Remoortel, D'haeseleer, Peeters, Cambron, Keyser, et al. 2019; Fragoso, Wille, Abreu, Brooks, Dias, Duarte, Farage, Finkelsztejn, Frohlich, Goncalves, Guedes, Medeiros, Oliveira, Ribas, da Rocha, Santos, Scorcine, da Silveira, Spedo, Tauil, Varela, and Vieira 2017; Golan et al. 2020a; D. Horakova et al. 2020).

The table below includes details on the validation studies that have been undertaken to demonstrate ico**brain ms** technical performance**.** ***Please note that MSmetrix (used in some publications) is a previous name for what is currently branded as icobrain ms.***

Table 2: Evidence of preclinical data

Evidence of ico**brain ms** performance supporting value claim "High accuracy and reliability"
1). Reference: (Jain et al. 2015b) **Type and objective of the study:** Validation Study of ico**brain ms** cross-sectional pipeline to quantify volume lesions **Intervention and comparator:** ico**brain ms** (machine learning version) compared to expert delineation and state of the art publicly available softwares: Lesion Segmentation Toolbox (LST) and Lesion-TOADS **Outcomes:** Accuracy of lesions volume using expert quantification as reference; reproducibility comparing agreement between two scans taken in a short interval ico**brain ms** compared favorably with comparators and showed good volumetric agreement (ICC=0.8) with expert quantification **Cohort:** Clinically acquired MRI scans from 20 MS patients from one centre in Netherlands (Accuracy dataset) and from 10 Patients from one hospital in Belgium scanned twice in a short interval (Reproducibility dataset) **2). Reference**:(Jain et al. 2016) **Type and objective of the study:** Validation Study of ico**brain ms** long pipeline (lesions evolution = difference in volume between two time points) **Intervention and comparator:** ico**brain ms** (machine learning version) compared to expert delineation and state of the art publicly available software LST-long **Outcomes:** Accuracy of new, disappearing, enlarging and shrinking lesions using expert quantification as reference; Reproducibility evaluated by agreement at both time points ico**brain ms** long pipeline is accurate and consistent in segmenting MS lesions compared to expert lesion segmentation. Also, it compares favorably with the publicly available software LST-long. **Cohort:** Clinically acquired MRI from 12 RRMS patients each scanned twice at an interval of approx. one year. (Accuracy dataset), and from 10 MS patients scanned twice on 3 different scanners (Reproducibility dataset). **3). Reference**: (D. Smeets et al. 2016) **Type and objective of the study:** Validation study of ico**brain ms cross/long** pipeline for measuring whole-brain and grey matter atrophy **Intervention and comparator:** ico**brain ms** cross and long pipeline compared to the state of the art publicly available state-of-the-art software SIENAX (which has already been used as surrogate outcome measure in several MS clinical trials). **Outcomes:** Test-retest measurement error on images acquired on the same scanner and the same day. Robustness toward physiological changes on MR images acquired at two successive time points from the same (healthy) subject Consistency of the atrophy measurements over time (3 time points with a time gap of at least 6 months)**.** When compared with SIENAX**, icobrain ms** had smaller measurement errors and higher robustness toward daily physiological changes while similar consistency in the measurement of longitudinal changes of brain atrophy. **Cohort:** Clinically acquired MRI from 10 MS patients from one hospital in Belgium scanned twice on 3 different scanners (measurement error dataset); a total of 120 T1- weighted images were acquired from 3 healthy subjects (40 scans/subject). Each subject was scanned two times on 20 different days within a 31- day period (Robustness dataset); brain MR images 20 MS patients from the department of radiology of the General University Hospital in Prague scanned on the same scanner at months 0,6,12 and 24 using the same protocol (Reproducibility dataset)

Table 2: Evidence of preclinical data (continued)

4). Reference: (C. Wang et al. 2016a)
Type and objective of the study: Validation study of cross-sectional whole brain volume measurements
Intervention and comparator: ico**brain ms** vs the competitor NeuroQuant software (CorTechs Labs) using SIENAX as reference, a well- validated cross-sectional tool that has been used extensively in MS clinical studies.
Outcomes: Whole brain volume (WBV), statistical precision (sp) and accuracy (sa) was evaluated. ico**brain ms** (sp=0,99, sa=0,99) and NeuroQuant (sp=0,98, sa=0,87) both quantified cross-sectional WBV with comparable statistical agreement to SIENAX. ico**brain ms** and NeuroQuant showed respectively a 1.0% and 5,5% volume 'overestimation' compared with SIENAX.
Cohort: Scans from 61 patients with RRMS and 2 patients with clinically isolated syndrome fulfilling McDonald 2010 criteria for MS. Patients able to have MRI were consecutively recruited from a single MS clinic in Sydney, Australia. Characteristics of patient at baseline: female 82,5, mean age 38, mean age at diagnosis 32, mean disease duration 8, mean Expanded Disability Status Scale (EDSS) of 2.
5). Reference: (A. Tsang et al. 2018)
Type and objective of the study: Validation (scan-rescan) study of ico**brain ms** whole brain volume measurement in a routine clinical environment.
Intervention and comparator: ico**brain ms** cross sectional and longitudinal whole brain volume measurements compared to the following softwares:
Cleveland Clinic (CCF; brain parenchymal fraction [BPF])4-5
– Siemens Healthcare (SMS; MorphoBox-Tempo prototype; BPF); – NeuroQuant (NQ; whole BV [WBV])6
– NeuroRx (NRX; normalised BV from SIENAX, calculated for Scan 1 only], and PBVC Jacobian integration)
Outcomes: The Jacobian integration approach implemented in ico**brain** has significantly lower scan-rescan measurement error (0.19%) compared to cross-sectional approaches for computing brain volume change such as NeuroQuant (0.4%). The ico**brain** error is comparable to the physiological (between-day) variability (0.20%).
Cohort: 30 MS patients from 3 MS PATHS participating health care institutions (Cleveland clinic, Johns Hopkins University, New York University) were recruited to participate in this scan-rescan study. Each patient was imaged 4 times within 1 week over 2 visits (2 MRIs at each visit) on 2 different Siemens 3T scanners. 57% were female, mean age 39,3, Mean Patient Determined Disease Steps (PDDS) PDDS 2,7, Mean disease duration 10,2.
6). Reference: (Lysandropoulos et al. 2016a)
Type and objective of the study: Validation study of ico**brain ms** WBV measurements MRI clinical acquired scans.
Intervention and comparator: ico**brain ms** brain volume measurements were compared with state-of-the-art SIENA software (FSL), a widely used software for research purposes.
Outcomes: ico**brain ms** median percentage error of the brain volume measurement between a 1.5T and a 3T scanner is 0.52% for Grey matter and 0.35% for Parenchymal Volume. For Siena this error equals 2.99%. When data of the same scanner are compared, the error is in the order of 0.06-0.08% for both ico**brain ms** and Siena.
Cohort: A total 18 MS patients (12 RRMS, 6 SPMS and 1 PPMS) were scanned on the same day on a 1.5T and a 3T scanner. Inclusion criteria were MS diagnosis according to McDonald Criteria 2010 and no MRI contraindication. The mean age was 40 years old and 77% were female. The mean EDSS was 3.1. The mean disease duration was 10 years.

Table 2: Evidence of preclinical data (continued)

7). Reference: (H. N. Beadnall et al. 2019a)
Type and objective of the study: Validation study of ico**brain ms** whole brain volume (WBV) measurement in a routine clinical environment.
Intervention and comparator: ico**brain ms** longitudinal percentage brain volume change (PBVC) measurements were compared with state-of-the-art SIENA software in a real-world multiple sclerosis clinical practice cohort
Outcomes: PBVC Statistical correlation, agreement and consistency between methods was evaluated. ico**brain ms** quantified longitudinal WBA with a strong level of statistical agreement and consistency compared to SIENA in this real-world MS population.
Cohort: A total of 102 patients were recruited from a single MS clinic in Sydney, Australia. At baseline, 99 subjects had RRMS, 2 had SPMS and 1 had clinically isolated syndrome (CIS). Patients were scanned twice with an average time gap of 1 year.
8). Reference: (Rakić, Vercruyssen, Van Eyndhoven, la Rosa, et al. 2021)
Type and objective of the study: Validation of ico**brain ms 5.1** improved version for lesions detection
Intervention and comparator: ico**brain ms 5.1** which combines unsupervised and supervised approaches to improve lesions detection is compared to ico**brain ms 5.0** which uses only an unsupervised approach. The validation was done by a panel of expert raters.
Outcomes: Lesion detection rates were compared using expert delineation as ground truth**.**
icobrain ms 5.1 improved detection of infratentorial and juxtacortical lesions by 14% and 31% respectively compared to ico**brain ms 5.0**
Cohort: The dataset consists of real-world pre-contrast T1 and FLAIR MS patient brain scans. The data is a multi-center and multi-scanner sample of real-world clinical data. The dataset consisted of scans from 51 patients with age range 20, 70 of which 61% were female
9). Reference: (Dirk Smeets 2023)
Type and objective of the study: Investigating multi-scanner reproducibility of ico**brain ms 5.10** improved version for brain structure segmentation
Intervention and comparator: ico**brain 5.10** is equipped with a full deep learning based brain segmentation algorithm in effort to achieve consistent results across MR images acquired in different settings. Test-retest reproducibility in comparison to FastSurfer and the previous version of the ico**brain** software (5.9) was evaluated.
Outcomes: Performance was measured in terms of absolute difference between the estimated volumes of each acquisition session and is compared to ico**brain 5.9** and Fastsurfer.
Cohort: The dataset consisted of T1 and FLAIR images of 10 MS patients., who were scanned twice with repositioning in three scanners.
10). Reference: (Smeets 2023)
Type and objective of the study: Validation of the use of real-world data on which ico**brain ms** was run in clinical practice as an additional reference population for patients with MS when evaluating whole brain volume.
Intervention and comparator: an ico**brain ms** population graph was built. Subsequently, age-matched percentiles for an independent MS dataset were computed for whole brain volume against the original healthy reference population and the ico**brain ms** population.
Outcomes: WBVs of MS subjects were less biased when represented on the ico**brain ms** population graph, which gives credibility to the representativeness of this population.
Cohort: The healthy reference population consisted of MRIs from 1069 healthy females and 834 healthy males, whereas the ico**brain ms** population consisted of 16021 real-world clinical brain MRI scans. The independent validation dataset consisted of 625 MRIs from 90 MS patients.

Table 2: Evidence of preclinical data (continued)

11). Reference: Ribbens 2023 **Type and objective of the study:** Validation of the use of real-world data on which ico**brain ms** was run in clinical practice as a reference population for lesion load in patients with MS. **Intervention and comparator:** an ico**brain ms** population graph was built for lesion volumes based on real-world data analysed using ico**brain ms** and validated using an independent dataset of MS patients of various clinical subtypes. **Outcomes:** Comparison against suitable populations could provide interpretable references for brain lesion volume measurements, which may be useful in the clinical follow up of MS patients. **Cohort:** The healthy reference population consisted of MRIs from 1069 healthy females and 834 healthy males, whereas the ico**brain ms** population consisted of 16021 real-world clinical brain MRI scans. The independent validation dataset consisted of 625 MRIs from 90 MS patients diagnosed with CIS (n = 12), RRMS (n = 30), SPMS (n = 28) or PPMS (n = 20).

5.3 Clinical data

The table below includes details of pilot studies investigating the comparative clinical usefulness of ico**brain ms** (D. Sima et al. 2018; Diana M. Sima et al. 2020; in Van Hecke et al. 2021a) (Van Hecke et al. 2019; H. Beadnall et al. 2017; H. N. Beadnall et al. 2018).

Table 3: Evidence of clinical data

Evidence of the impact of ico**brain ms** on radiology workflow, detection of disease activity status and DMT clinical decision-making supporting value claims "**Greater radiology efficiency and capacity**" and "**Increased consistency of radiology report and reduced skill gap" "Increased clinical relevance of radiology report to allow timely clinical decision making"**
1). Reference: (D. Sima et al. 2018) **Type and objective of the study:** Pilot test and retest experiment to assess the impact of ico**brain ms** on lesion detection, count and consistency in a clinical trial setting. **Intervention and comparator:** MS lesion detection and counts with aid of ico**brain ms** that performed by compared with performed by MS professionals without ico**brain ms** **Outcomes:** Time per evaluation and inter and intra -rater agreement. ico**brain ms** enhances and significantly speeds-up visual lesion detection and count. The timing differed significantly between the task of performing lesion count without (mean ± SD: 54.3 ± 11.8 min), or with ico**brain ms** (mean ± SD: 26.7 ± 19.8 min). Intra-rater test-retest lesion count agreement on scan and rescan images was significantly improved for the assistant neurologist, from a standard deviation (SD) of the differences between test and retest lesion counts of 28.1 without ico**brain ms** to 22.0 with ico**brain ms** (improvement of 21.7%), but was constant for the experienced radiologist (SD = 7.3 in both scenarios). Larger changes were observed in the case of inter-rater agreement: without ico**brain ms** annotations, inter-rater lesion count agreement between experienced radiologist and assistant neurologist was significantly worse (SD = 20.8) than with ico**brain ms** (SD = 15.7), indicating an improvement of 32.5% by using ico**brain ms**. **Cohort:** Two raters (an experienced Experienced radiologist and an assistant neurologist) assessed clinically acquired MRI images from 10 MS patients.

Table 3: Evidence of clinical data (continued)

2). Reference: (Diana M. Sima et al. 2020)
Type and objective of the study: Pilot study assessing the value of ico**brain ms** prepopulated report on MS follow-up
Intervention and comparator: ico**brain ms** prepopulated reporting including lesion load (including new and enlarging lesions) and brain volumetry (including annualized atrophy) was compared to standard radiological reporting.
Outcomes: The two radiological reporting scenarios (without and with volumetric software results) were compared in terms of effect on diagnostic findings i.e. disease activity status and timing.
ico**brain ms** assisted reporting is more sensitive than standard radiological reporting in detecting disease activity: the percentage of pwMS deemed as having (slight) disease activity or progression grew from 24% in conventional reading to 76% (44% active, 32% slightly active, according to specified clinical definitions) with the ico**brain ms** assisted reading. With respect to timing, radiological reporting took on average 7 min 28 s (SD: 3 min 6 s) without ico**brain ms** and 5 min 49 s (SD: 2 min 15 s) with ico**brain ms** (improvement by about 40%). In other words, computer-aided radiological reporting with ico**brain ms** was thus faster than conventional reporting, and allowed to generate approximately 8 conventional reports per hour versus 13 computer-aided reports per hour, which is an improvement by about 60%.
Cohort: Longitudinal clinical MRI acquisitions approximately 1 year apart were collected from 25 multiple sclerosis patients. Each MRI dataset, which included images from two time points, was presented in random order to an experienced radiologist twice: once without and once with an ico**brain ms** report.
3). Reference: (Van Hecke et al. 2019)
Type and objective of the study: Pilot study assessing the value of ico**brain ms** pre-populated report on MS lesion detection and count.
Intervention and comparator: ico**brain ms** quantitative assessment for new or enlarging lesions at baseline and at 1year follow-up was compared with 1) standard clinical report, 2) structured radiological report assessed by a neuro-radiologist and 3) local automated measurements.
Outcomes: New or enlarging lesions count at baseline and at 1year follow-up accuracy and agreement between assessment methods. ico**brain ms** showed an increase in lesions detection sensitivity by 32% compared to the other assessment methods. Moreover, it agrees well (80%) with manual counts both in terms of classification (presence/absence) as in absolute number of new/enlarging lesions.
Cohort: MRI scans approximately 1 year apart were collected from 100 (RRMS or SPMS) originating from two centres.
4). Reference: (H. Beadnall et al. 2017)
Type and objective of the study: Retrospective longitudinal study to assess the impact of ico**brain ms** assisted assessment on disease activity status in clinical practice
Intervention and comparator: ico**brain ms** quantitative MRI assessment (lesion and whole brain atrophy) was compared to 1) expert neuro-radiologist visual review and 2) local quantitative MRI (qMRI) pipeline
Outcomes: Disease activity according to NEDA-3 (clinical and lesion) and NEDA-4 (clinical, lesion and brian atrophy) criteria. ico**brain ms** had the highest increase in NEDA-3 by about 14% compared to both local QMRI and radiological assessment. ico**brain ms** and local QMRI had similar increases by about 48% on NEDA-4 status compared to the radiological assessment.
Cohort: Clinically acquired MRI images from 150 MS patients (98% RRMS) at baseline and at 1year follow-up: 77,3% female, at baseline mean age 38,8y, mean disease duration 9 y, average EDSS score 2. MRI assessment was made by neuro-radiologists from 3 centres located in Buffalo (USA), Prague (Czech Republic) and Sydney (Australia).

Table 3: Evidence of clinical data (continued)

5). Reference: (H. N. Beadnall et al. 2018)
Type and objective of the study: Pilot Retrospective longitudinal study to assess the impact of ico**brain ms** assisted assessment on DMT decision making in MS clinical practise
Intervention and comparator: ico**brain ms** fully automated report compared with standard clinical report.
Outcomes: Disease activity status and clinical decision (DMT change or earlier clinical and MRI follow-up) were recorded via a questionnaire. The study showed that ico**brian ms** has the potential to influence DMT decision making regarding disease activity assessment and DMT changes (from 16,1% to 32,3%). In addition, earlier MRI follow-up would be considered in 41,9% of cases.
Cohort: Clinical MS brain MRI scans (separated by one-year minimum, acquired on the same scanner from the same patient) were evaluated. 31 relapsing-MS patients (77.4% female), with baseline age 42.14 years, disease duration 7.6 years and EDSS score 1.40 (1.36).
6). Reference: (Diana M. Sima et al. 2021)
Type and objective of the study: A microsimulation study to assess the Health Economic Impact of Software-Assisted Brain MRI on Therapeutic Decision-Making and Outcomes of Relapsing-Remitting Multiple Sclerosis Patients
Intervention and comparator: A simulated decision analytical model was developed based on a hypothetical cohort of RRMS patients to compare a baseline decision-making strategy in which only clinical evolution (relapses and disability progression) factors are used for therapy decisions in MS follow-up, with decision-making strategies involving MRI. In this context, we include comparisons with a visual radiologic assessment of lesion evolution, software-assisted lesion detection, and software-assisted brain volume loss estimation. The model simulates clinical (EDSS transitions, number of relapses) and subclinical (new lesions and brain volume loss) disease progression and activity, modulated by the efficacy profiles of different DMTs. The simulated decision-making process includes the possibility to escalate from a low efficacy DMT to a high efficacy DMT or to switch between high efficacy DMTs when disease activity is detected. We also consider potential error factors that may occur during decision making, such as incomplete detection of new lesions, or inexact computation of brain volume loss. Finally, differences between strategies in terms of the time spent on treatment while having undetected disease progression/activity, the impact on the patient's quality of life, and costs associated with health status from a US perspective, are reported.
Outcomes: The average time with undetected disease progression while on low efficacy treatment is shortened significantly when using MRI, from around 3 years based on clinical criteria alone, to 2 when adding visual examination of MRI, and down to only 1 year with assistive software. Hence, faster escalation to a high efficacy DMT can be performed when MRI software is added to the radiological reading, which has positive effects in terms of health outcomes. The incremental utility shows average gains of 0.23 to 0.37 Quality Adjusted Life Years (QALYs) over 10 and 15 years, respectively, when using software-assisted MRI compared to clinical parameters only. Due to long-term health benefits, the average annual costs associated with health status are lower by $1500–$2200 per patient when employing MRI and assistive software.
Cohort: A hypothetical cohort of 1000 RRMS patients (female to male ratio 3:1) is simulated from the moment they start therapy on a low efficacy DMT.

Table 3: Evidence of clinical data (continued)

7). Reference: (Van Hecke et al. 2021a) **Type and objective of the study:** To present a Novel Digital Care Management Platform to Monitor Clinical and Subclinical Disease Activity in Multiple Sclerosis consisting of (1) a patient phone / web application and healthcare professional portal (ico**mpanion**) including validated symptom, disability, cognition, and fatigue patient-reported outcomes; and (2) clinical brain magnetic resonance imaging (MRI) quantifications (ico**brain ms**). **Intervention and comparator:** Both tools (ico**mpanion** and ico**brain ms**) were validated using their ability to detect (sub)clinical disease activity (known-groups validity) and real-world data insights. **Outcomes**: Surveys showed that 95.6% of pwMS were interested in using an MS app, and 98.2% were interested in knowing about MRI changes. The ico**mpanion** measures of disability ($p < 0.001$) and symptoms ($p = 0.005$) and ico**brain ms** MRI parameters were sensitive to (sub)clinical differences between MS subtypes. ico**brain ms** also decreased intra- and inter-rater lesion count variability and increased sensitivity for detecting disease activity/progression from 24% to 76% compared to standard radiological reading. This evidence shows pwMS' interest, the digital care platform's potential to improve the detection of (sub)clinical disease activity and care management, and the feasibility of linking different digital tools into one overarching MS care pathway

5.4 Rationale

Current research in the area of MRI monitoring of pwMS is mostly focused on the impact of MRI quantification tools on radiology workflow efficiency and consistency. Moreover, the majority of the evidence is from retrospective studies and evidence from real world clinical practice is very limited. The latter also applies to the impact of AI-tools on clinical decision-making, patient outcomes and healthcare costs. The existing body of evidence of ico**brain ms** includes pilot and retrospective studies which do not reflect real world clinical practice and are potentially subject to bias, and so far, there has been no assessment of the technology in the NHS. In particular, more prospective comparative studies are needed to evaluate the patient benefits of the technology in the NHS setting, as recommended by NICE in a recently published Medtech Innovation Briefing (MIB)-(NICE 2022). The MIB was based on six studies (three non-randomised comparative studies, and three technical validation studies) and underscored the potential benefits of the implementation of the tool in the NHS setting. Nonetheless, key uncertainties at this time are that the evidence is limited in quantity and quality, and primarily assesses the technical validity of the technology. There is no evidence for its use in the NHS. AssistMS will fill this gap by providing prospective, randomised, real world evidence of the clinical usefulness of ico**brain ms** including the impact on the patient care pathway and outcomes.

We will conduct a prospective clinical study to compare ico**brain ms**-assisted MRI to the current Standard of Care (SoC) in assessing disease activity. The Interventional arm is defined by 'radiological reading by a neuro-radiologist assisted by ico**brain ms.** The SoC arm is defined by 'radiological reading by a neuro-radiologist'. When describing SoC, the aim of the trial is not to provide a proscribed list of how a neuro-radiologist should read an MRI for this study, but to allow them to operate as they normally would.

The main objectives and outcomes of the study are the following:

1. **Primary objective:**

- To assess the clinical usefulness of ico**brain ms** by evaluating the detection of disease activity (as defined by new and/or expanding lesions): what proportion of patients have disease activity detected when ico**brain ms** is being employed, alongside the visual assessment, compared to SoC assessment by a (neuro)radiologist.

2. **Secondary objectives (Clinical):**

- To assess the clinical usefulness of ico**brain ms** by evaluating the presence of brain volume loss: what proportion of patients have brain volume loss detected when ico**brain ms** is being employed, alongside the visual assessment, compared to standard of care assessment by a (neuro)radiologist.
- To assess the contribution of ico**brain ms** to treatment switch decisions as reflected by the proportion of treatment initiation or switch decisions with or without ico**brain ms**
- To assess the impact of ico**brain ms** on patient outcomes by evaluating the difference in the number of relapse(s) between ico**brain ms** and SoC
- To assess the contribution of clinical change in decision making by evaluating the difference in proportion with clinical change between the interventional arm and SoC
- To assess the efficiency of radiologists by evaluating the difference in radiological reporting time with or without ico**brain ms**

3. **Secondary objective (Health Economics):**

- To assess the cost-effectiveness of MS patient management strategy when ico**brain ms** is being employed, alongside the visual assessment, compared to SoC assessment by a (neuro)radiologist

4. **Tertiary objective:**

- To assess the contribution of ico**brain ms** to switch decisions by evaluating the impact of ico**brain ms** on the proportion of patients with treatment initiation or switch decisions in those with or without clinical deterioration.

5. **Exploratory objectives:**

- To assess the level of agreement between radiologists with and without neurological specialisation
- To assess the contribution of MRI change in decision making

5.5 Risks / benefits

5.5.1 Risks

ico**brain ms** is a medical device which supports the HCP by providing additional information. The device itself has no direct impact on the patient and is only meant to support the HCP to make treatment decisions. These treatments will be those which are used in standard clinical practice.

ico**metrix** ensures risks are properly followed up using the standard operating procedures (SOPs) (see section 10 for details on risks). We therefore plan to follow the ico**metrix** SOPs which would include any relevant yellow card and MIR submissions to the MHRA. Due to the nature of both ico**brain ms** and the study design, we will not collect clinical Adverse Events (AEs) or Serious Adverse Events (SAEs) that would normally be needed for a CTIMP or other interventional study. The ico**brain ms** software will not be making independent 'decisions' on behalf of patient care (no drugs are tested as part of the study and are all used as approved on-label). There are no direct risks and harms associated with using ico**brain ms**. ico**brain ms** was deemed acceptable by regulatory bodies for use in clinical practice and has a Conformité Européenne (CE) mark.

The indirect risks are primarily related to data protection which are covered and discussed in Sec 10.

5.5.2 Benefits

1. Optimization and standardisation of image acquisition protocols:

ico**brain ms** allows objective measurement of scan quality (scan parameters image contrast, brain coverage, scan angle, etc) and comparison to guidelines (CMSC, MAGNIMS) and to a global image quality benchmark (Vercruyssen et al. 2020).

2. High accuracy and reliability:

ico**brain ms** delivers accurate quantitative measurements of brain lesions and brain atrophy to monitor subtle and relevant clinical changes(C. Wang et al. 2016b; Finkelsztejn, Fragoso, et al. 2018; Lysandropoulos et al. 2016b; Akaishi et al. 2020b; D'hooghe, Gielen, Van Remoortel, D'haeseleer, Peeters, Cambron, De Keyser, et al. 2019; Fragoso, Wille, Abreu, Brooks, Dias, Duarte, Farage, Finkelsztejn, Frohlich, Goncalves, Guedes, Medeiros, Oliveira, Ribas, da Rocha, Santos, Scorcine, da Silveira, Spedo, Tauil, Varela, Vieira, et al. 2017; Golan et al. 2020b; Dana Horakova et al. 2020; Y. P. Tsang et al. 2014; Dirk Smeets et al. 2016; D. M. Sima, Billiet, Vyvere, and Maertens 2017; Rakić, Vercruyssen, Van Eyndhoven, de la Rosa, et al. 2021; Jain et al. 2016, 2015a; H. N. Beadnall et al. 2019b).

3. Greater radiology efficiency and capacity:

ico**brain ms** increases radiologist efficiency (+40%), reducing interpretation time and generating more reports (+60%) with existing resources (Van Hecke et al. 2021b).

4. Increased consistency of radiology report and reduced skill gap:

ico**brain ms** creates more structured [pre-populated] radiology reports increasing intra- and inter-reader consistency for greater reliability of imaging results: 21.7% improvement of intra-reader agreement and 32.5% improvement of inter-rater agreement(Van Hecke et al. 2021b).

- Reduced Health inequalities: ico**brain ms** can help to reduce health inequalities that are due to variation in MS expertise and sub-specialisation across the NHS.

5. Increase clinical relevance of radiology report to allow timely clinical decision making:

ico**brain ms** enables accurate detection of disease activity (from 24% to 76% compared to standard visual assessment) and stage for timely therapy decisions (increment of switchings from 16% to 32%) which can lead to a reduction of time on suboptimal treatment (Van Hecke et al. 2021b; Heidi N. Beadnall et al. 2018).

6. Improve patient outcomes and reduce total cost of care:

ico**brain ms** provides clinicians with valuable insights on disease activity and status, accelerating time to optimal treatment, which can improve patient outcomes (Giovannoni et al. 2016b) and a reduction of health and other care costs associated with neurological disability. An initial cost-effectiveness analysis on integrating ico**brain ms** into the NHS monitoring/switching decision pathway indicates that ico**brain ms**-assisted MRI assessment could generate an incremental QALYs gain of 0.19 and incremental cost savings, not accounting for the extra cost of ico**brain ms**, of £ 5776 per patient over a time-horizon of 20 years. Incremental cost savings were driven largely by health care (EDSS and relapse related) and DMT costs, and incremental QALY gain largely by differences in delayed EDSS progression and reduction in annual relapse rate (Esposito et al. 2022).

6. Study Objectives, Outcomes and Endpoints

6.1 Definitions of Clinical Trial Arms

The Interventional arm is defined by 'radiological reading by a neuro-radiologist assisted by ico**brain ms'.** The SoC arm is defined by 'radiological reading by a neuro-radiologist'.

6.2 Primary clinical objective

To assess the clinical usefulness of ico**brain ms** by evaluating the detection of disease activity (as defined by new and/or expanding lesions): what proportion of patients have disease activity detected when ico**brain ms** is being employed, alongside the visual assessment, compared to SoC assessment by a (neuro)radiologist.

6.3 Secondary objectives

To assess:

- The clinical usefulness of ico**brain ms**
- The contribution of ico**brain ms** to treatment initiation or switch decisions
- The impact of ico**brain ms** on patient outcomes
- The efficiency of radiologists reporting MRI scans in the context of pwMS follow-up
- The cost-effectiveness of ico**brain ms**

6.4 Tertiary objective

- To assess the contribution of clinical change and radiological reading with and without ico**brain ms** into treatment decision making

6.5 Exploratory objective

To assess:

- The impact of ico**brain ms** on the level of agreement on radiological review between expert neuro-radiologists and general radiologists without sub-speciality training.
- the contribution of MRI change in decision making.

6.6 Primary clinical endpoint

Difference in proportion with disease activity between the interventional arm and SoC based on baseline-year 1 and/or, where available, retrospective-baseline. For those trial participants with a retrospective MRI scan usable by ico**brain ms**, the difference in disease activity can be measured between this scan and the baseline (M0) MRI scan. In addition, the difference in disease activity will be measured between the baseline (M0) and final (M12) scan).

6.7 Secondary endpoints

- Difference in proportion with brain volume loss between interventional arm and SoC based on baseline-year 1 and/or, where available, retrospective-baseline
- Difference in proportion of treatment initiation or switch decisions between interventional arm and SoC based on baseline-year 1 and/or, where available, retrospective-baseline
- Difference in the number of relapse(s) between interventional arm and SoC from baseline to year 1
- Difference in proportion with clinical deterioration, stability or improvement between interventional arm and SoC based on baseline-year 1
- Difference in mean time (minutes/seconds) to produce a radiologist-authorised MRI brain report between interventional arm and SOC.
- Incremental cost per quality-adjusted life year (QALY) gained with use of ico**brain ms**

6.8 Tertiary endpoint

- Impact of ico**brain ms** on the proportion of patients with treatment initiation or switch decisions in those with or without clinical deterioration

6.9 Exploratory endpoints

- The ratio of Krippendorff's Alpha for the agreement between expert neuroradiologists and general radiologists with and without ico**brain ms**
- Difference in proportion with treatment switch/initiation for those with and without MRI change (atrophy or lesions) in the interventional arm and SoC arm based on baseline-Year 1 and/or, where available, retrospective-baseline.

6.10 Summary table of objectives, endpoints and related outcomes

The objectives, outcomes and subsequent endpoints are additionally reflected in the table below.

Table 5: Summary table of objectives, endpoints and outcomes

	Objective	Outcome	Endpoint
Primary	To assess the clinical usefulness of ico**brain ms**	Disease activity reflected by; new and/or expanding MS lesions on brain MRI	Difference in proportion with disease activity between the interventional arm and SoC based on baseline-year 1 and/or, where available, retrospective-baseline. *
Secondary	To assess the clinical usefulness of ico**brain ms**	Presence of brain volume loss (yes/no)	Difference in proportion with brain volume loss between interventional arm and SoC based on baseline-year 1 and/or, where available, retrospective-baseline*
	To assess the contribution of ico**brain ms** to switch decisions	Treatment initiations/switches at baseline and year 1 visits	Difference in proportion of treatment initiation or switch decisions between interventional arm and SoC based on baseline-year 1 and/or, where available, retrospective-baseline*
	To assess the impact of ico**brain ms** on patient outcomes	Clinical relapse(s)	Difference in the number of relapse(s) between interventional arm and SoC from baseline to year 1
	To assess the impact of ico**brain ms** on patient outcomes	Clinical change as reflected in: - WebEDSS/EDSS - T25ftWT - 9HPT - SDMT/SST - NfL	Difference in proportion with clinical deterioration, stability or improvement between interventional arm and SoC based on baseline-Year 1
	To assess the efficiency of radiologists reporting MRI scans in the context of pwMS follow-up	Difference in radiological reporting time with/without ico**brain ms**	Difference in mean time (minutes/seconds) to produce a radiologist-authorised MRI brain report between interventional arm and SoC
	To assess the cost effectiveness of ico**brain ms**	Incremental cost per quality-adjusted life year (QALY) gained with compared to without ico**brain ms**	The ratio of Incremental cost and incremental quality-adjusted life year (QALY) with compared to without ico**brain ms**

Table 5: Summary table of objectives, endpoints and outcomes (continued)

	Objective	Outcome	Endpoint
Tertiary	To assess the contribution of clinical change and radiological reading with and without ico**brain ms** into treatment decision-making	Treatment initiations/switches at baseline and year 1 visits	Impact of ico**brain ms** on the proportion of patients with treatment initiation or switch decisions in those with or without clinical deterioration.
Exploratory	The impact of ico**brain ms** on the level of agreement on radiological review between expert neuroradiologists and general radiologists without subspecialty training.	Krippendorff's Alpha for agreement between neuro-radiologists and general radiologists	The ratio of Krippendorff's Alpha for the agreement between expert neuroradiologists and general radiologists with and without ico**brain ms**
	To assess the contribution of MRI change in decision making.	MRI deterioration of MRI lesions and atrophy	Difference in proportion with treatment switch/initiation for those with and without MRI change (atrophy or lesions) in the interventional arm and SoC arm based on baseline-Year 1 and/or, where available, retrospective-baseline. *

*Participants in whom retrospective data (MRI, clinical) can be included may do so at two time points (baseline and year 1), whilst participants in whom retrospective MRI and/or clinical measures are not available, will only provide data for this outcome at one time point (year)

7. Study population

Patients will be recruited from the neuro-inflammation services of the participating clinical trial sites. Potential participants will be identified by the Principal Investigator (PI) and other members of the clinical care teams from the caseload of patients under the care of each site's hospital or Trust. These will be patients that are due their MRI brain scans as per standard of care.

The associated baseline MRI visit must be scheduled within 12 weeks of the annual clinic visit (either before or after) in order for the potential participant to be entered into the trial. It is immaterial if the patient has the clinic visit or MRI visit first, as long as they are consented and randomised prior to the MDT where they will be discussed. This will ensure a good correlation of clinic and MRI timelines and help allow for the overall target to be met within the one year allotted. Potential participants will be initially approached by a member of the PIs team during their routine clinic visits or by phone or email. Participants who are initially contacted by phone/email will be given a summary of what the study involves and a preliminary assessment of interest and eligibility. Potential participants can also be given a link to the Castor website which will be set up with basic information around the trial, as well as the Patient Information Sheet (PIS)/Informed Consent (IC). They can register their interest there.

Those who are not interested, or ineligible, will therefore be spared further discussion when at the clinic. If potential participants are interested in receiving more information, they will be sent a copy of the PIS by post or email, or they may be given a copy during their clinic visit. Alternatively, potential participants can be given a link to the eConsent platform where they will be able to register their interest. Potential participants will be encouraged to ask any questions they have about the study and will be given as much time as they require to consider their participation in the trial before they sign the informed consent form (ICF).

Regardless of whether the initial contact is made by telephone/email, and whether the PIS was sent in the post or by email, or given in person initially, all participants will have a detailed discussion with a trained member of the research team before giving consent or e-consent via the Castor web based eConsent platform. Participants will be formally assessed for inclusion at this same screening visit, following IC.

7.1 Inclusion criteria

Inclusion criteria are:

- 18-99 years of age
- Clinically Isolated Syndrome suggestive of demyelination (CIS) or definitive diagnosis of MS
- Undergoing MRI head investigation
- On an MS DMT pathway
- Access to a smartphone, tablet or computer

7.2 Exclusion criteria

The single exclusion criterion is: pwMS participating in a randomised controlled CTIMP (pwMS participating in a single arm study may be included, provided this is in line with the other protocol).

7.3 Vulnerable participant considerations

Due to the severity of the disease, some participants with a higher EDSS rating may have some degree of cognitive impairment and may be considered as vulnerable participants as per the NHS England safeguarding guidelines (NHS England » Safeguarding). Whilst vulnerable participants will be included in this study, all participants, including those who are vulnerable, must have capacity.

The PI is responsible for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

8. Study design

This is a prospective randomised controlled clinical study. Participants in AssistMS will be individually randomised following IC.

Data collection will be via electronic Case Report Form (eCRF) entered by research teams, radiologists and the trial participants themselves (*via* Patient Reported Outcomes (PROs) and a Resource Use Questionnaire.) In addition, patient consent will be obtained to access their hospital records data for the period from 6 months prior to randomisation to the end of follow-up in the study.

For the NHS England DAR datasets, relevant participant PID and their trial ID will be sent directly from each trial site to a safe haven server within QMUL. At the end of the study, all this collected PID will then be sent to NHS England for data extraction. Details are in Sec 9.6.

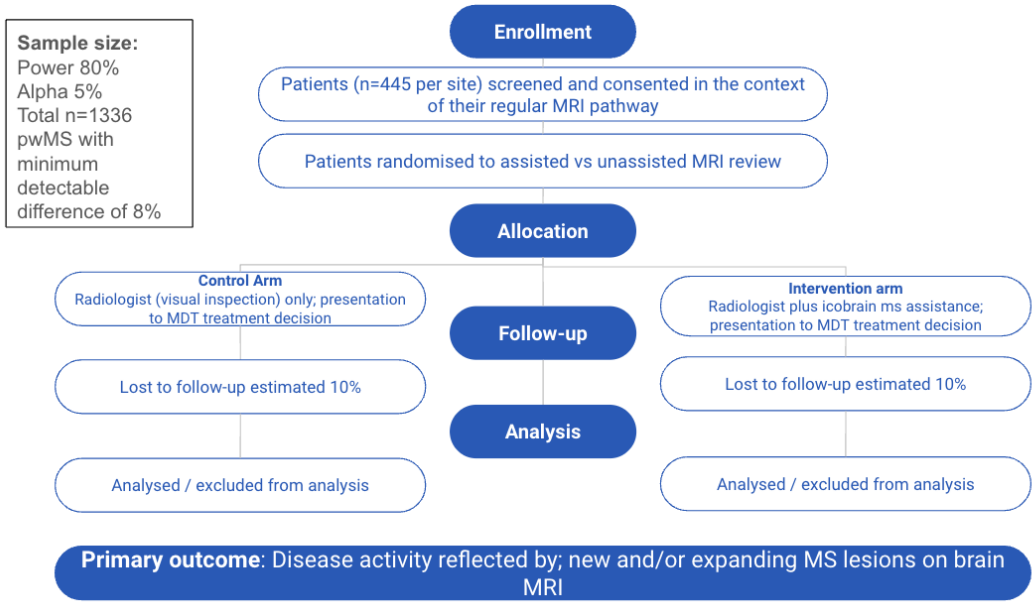


Figure 1: Study Design

9. Study procedures

Please note the following with regards to study procedures. We will be engaging with Castor EDC with most trial related data management and informed consent. This will encompass electronic informed consent (via a secure video link), randomisation, ePROs as well as the trial's CRFs.

9.1 Informed Consent Procedures

Informed consent must be obtained prior to the participant undergoing procedures or PROs that are specifically for the purposes of the trial and are outside standard routine care at the participating site (including the collection of identifiable participant data).

9.1.1 Responsibility for Obtaining Consent

The PI retains overall responsibility for the IC of participants at their site and must ensure that any person delegated responsibility to participate in the IC process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent occurs, then details should be provided in the Site Delegation Log. IC will be obtained by appropriately trained and experienced medically qualified staff.

9.1.2 Consent Considerations

The right of a participant to refuse participation without giving reasons will be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Where a participant is required to re-consent or following an amendment that affects the patient, or new information needs to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner. The consent will also consider those participants that may not wish to consent for the NHS England DARS datasets as discussed in Sec 9.6. Potential participants may selectively opt-out of these datasets however still be accepted onto the trial. This will be highlighted on the Castor website to ensure anyone that did not consent for DARS is treated accordingly.

The PI/sub-investigator will have to make the assessment of capacity. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. Where participants are capable of consenting for themselves but are particularly susceptible to coercion, the PI/sub-investigator will document how their interests will be protected.

9.1.3 Population

Male and female patients with either CIS or a definite diagnosis of MS who are 18+ years old. They must also be either on a DMT or under consideration for DMT. Participants must be able and willing to comply with protocol requirements. However, patients enrolled in a CTIMP trial (unless in an open-label single arm extension) cannot be considered for this study. Additionally, it will be the responsibility of the site PI or delegate to contact the PI/trial manager of the other study to obtain permission from them prior to consent. This permission should be documented within the patient's medical record and added to the appropriate section in the site's ISF.

9.1.4 Vulnerable Participant's Considerations

The PI takes responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

9.1.5 Written/Reading Translation Considerations

For participants who cannot read or write, a witness will be allowed to sign and/or date the eICF on behalf of the participant. For participants who are not fluent in English, the interpreter service present in each hospital/trust will be utilised. A member of the family or guardian/carer may be present, however they cannot act as an official interpreter with regards to obtaining informed consent. A face-to-face or telephone interpreter may be used, whichever is deemed appropriate by the PI or delegate. Once consent is granted, a carer or member of the family can attend any visits with the participants and translate as necessary.

9.1.6 Participants Lacking Capacity

Participants who do not have the capacity to provide IC will not be included in the trial.

9.1.7 Consenting Process

Potential participants will be encouraged to ask any questions they have about the study and will be given as much time as they require to consider their participation in the trial before they wet or electronically sign the ICF. A mandatory 24-hour requirement pre-review is not necessary with this study, however, all efforts will be made to ensure potential participants are sent the relevant documentation at least one day prior to their screening/baseline visit for review. The participant will be given the opportunity to discuss it with family and friends or primary care physician and to ask questions to the research team. The consent process will be documented in the medical notes/source document, including the date the trial was first discussed with the patient, the date the PIS was given (or accessed electronically) and the dates of any trial-related telephone or face-to-face discussions the PI/delegate has had with the patient before they agreed to participate and signed the ICF.

The date of consent must also be documented in the source document, along with the version and date of the PIS and ICF signed.

With the e-consent platform, the PI or delegate will have administrative access in order to document relevant information in the participant's hospital CRF.

The PI/sub-investigator will have to make the assessment of capacity. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves.

A capable person will:

- Understand the purpose and nature of the research
- Understand what the research involves, its benefits (or lack of benefits), risks and burdens
- Understand the alternatives to taking part
- Be able to retain the information long enough to make an effective decision
- Be able to make a free choice
- Be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity).

Where participants are capable of consenting for themselves but are particularly susceptible to coercion, the PI/sub-investigator will document in the patient's notes how their interests will be protected.

9.2 Screening and Baseline (Visit 1 during SOC appointment)

Screening procedures are detailed here and summarised in the schedule of events below. The screening and baseline visits are the same in this study. Following signing IC (wet signatures or e-consent), patients can then commence the screening procedure. Trial sites are aware that all participants that undergo screening are logged into a screening log associated with the study and that it is documented on the delegation log who is authorised to complete this task.

During the screening/baseline visit, participants will either discuss or answer the following or, if applicable, undergo the following tests as per the Trust's SoC visit:

- Year of MS Diagnosis, Age at MS Diagnosis, disease duration, MS Subtype (RMS, SPMS, PPMS) Current DMT (if applicable) and demographic information (DOB, Sex at birth, Gender, Ethnic group)
- Radiologist or clinic coordinator to upload latest retrospective head MRI (if available and useable for ico**metrix**)
- Review inclusion and exclusion criteria
- Randomisation
- If past head MRI is available, add correlating EDSS, NfL, 9HPT, T25FW and SDMT (if available)
- web-EDSS or clinical EDSS
- 9HPT (only if it is part of the participant's SoC)
- T25-FW (only if it is part of the participant's SoC)
- SDMT (only if it is part of the participant's SoC)
- SST (only if it is part of the participant's SoC)
- Neurofilament light level (Cerebral Spinal Fluid (CSF) or serum) (only if it is part of the participant's Standard of Care (SoC))
- Euroqol EQ-5D-5L (ePRO)
- Healthcare and Other Resource Use Questionnaire (ePRO)
- Relapse Review
- DMT Review
- MDT summary

Prior to randomising, documentation by the investigator that the clinical records were checked for all inclusion and exclusion criteria is required. The eCRF (Screening section) will run through these criteria as well (Sec 7.1-7.2)

A log of participants who are screened but not randomised should be documented. For CONSORT reporting, only those consented but not randomised should have demographic data (age, gender, ethnicity and disease duration)documented. If applicable, the reason for not undergoing randomisation should also be documented in the patients' medical notes.

9.3 Patient Allocation

9.3.1 Randomisation Method

Randomisation (using stratified randomisation): Randomisation will be performed by an authorised member of the research team at the site using the web-based randomisation service, developed and managed by Castor™. Eligibility and consent will be verified before each patient is randomised. Patients will be allocated into two equal groups: SoC/SoC+AI in a 1:1 ratio. Allocation will be by a computer using stratified randomisation with random permuted blocks using 3 categorical factors: Gender (M/F), MS subtype (RMS/CIS, PMS), and centre.

9.3.2 Randomisation Procedure

Eligible patients will be randomised after eligibility has been confirmed and the following information obtained (as described on the Schedule of Assessments and Sec 9.4.3):

- Year of MS Diagnosis (if patient has CIS, i.e. not MS, then that year should be recorded)
- Age at MS Diagnosis (if patient has CIS, i.e. not MS, then that age should be recorded)
- MS Subtype (RMS, SPMS, PPMS)
- Current DMT (if applicable)
- Past MRI head (if available and useable for ico**brain ms**) (Participants can still enter the study if there is no retrospective scan or if the retrospective scan is not useable for ico**metrix**)
- Demographic information

After reviewing the inclusion/exclusion criteria for eligibility, delegated members of the study team will perform the randomisation. A web-based randomisation system, developed and maintained by Castor™, will be used. Further details will be found in the study specific randomisation SOP.

9.3.3 Blinding

The study will not be blinded as it would not be possible to do so in this real-world study.

9.4 Study Interventions

Not all clinical tests that are part of this study are typically used during the MDT for decision-making. Nevertheless, they form part of the secondary outcomes. In case any relevant clinical test results are used during the MDT to support a decision, this will be added to the report by means of three tick boxes:

1. Was the decision by the MDT **mainly** driven by the MRI result? [Y/N]
2. Was the decision by the MDT **mainly** driven by clinical features? [Y/N]
3. Was the decision by the MDT driven by both the MRI result and clinical features? [Y/N]
4. Were any of the following factors involved with the MDT decision? [Tick all that apply]
    - None
    - EDSS
    - 9HPT
    - T25FW
    - SDMT
    - SST
    - NfL level
    - Other [free text]

9.4.1 Schedule of Treatment for each visit

Screening/clinical baseline procedures are detailed in Section 9.2 above. Procedures performed on all other study visits are listed here and summarised in the schedule of events in Section 9.5. Detail on particular procedures can be found in Section 9.6

Baseline Visit A (MRI related):

- Participant: Attend for Yearly MRI as per SoC
- Neuro-radiologist: Review MRI compared to previous MRI assessment (if applicable)

Month 6 ((Remote) Visit 2) (Participant):

- Euroqol EQ-5D-5L (ePRO)
- Healthcare and Other Resource Use Questionnaire (ePRO)

Year 1 (Visit 3 during SOC appointment) (Participant):

- web-EDSS or clinical EDSS
- 9HPT, provided this is the participant's SoC
- T25-FW, provided this is the participant's SoC
- SDMT, provided this is the participant's SoC
- SST, provided this is the participant's SoC
- Cerebral Spinal Fluid (CSF) or serum (s) Neurofilament light level (cNfL/sNfL), provided this is part of the participant's SoC
- EQ-5D-5L (ePRO)
- Healthcare and Other Resource Use Questionnaire (ePRO)
- Relapse Review
- DMT Review
- MDT Summary
- DARS Datasets

Year 1 (Visit B) (MRI):

- Participant: Attend for Yearly MRI as per SoC
- Neuro-radiologist: Review MRI compared to previous MRI assessment
- Neuro-radiologist: System Usability Scale

Early Withdrawal

In the event a participant is withdrawn from the study or chooses to withdraw, the most recent data will be obtained from their medical notes. It is important to note that a discrete visit will not be required in order to obtain this information.

- Document reason for withdrawal
- most recent web-EDSS or clinical EDSS (if different from baseline data point)
- 9HPT (if part of the participant's SoC) (if different from baseline data point)
- T25-FW (if part of the participant's SoC) (if different from baseline data point)
- SDMT (if part of the participant's SoC) (if different from baseline data point)
- SST (if part of the participant's SoC) (if different from baseline data point)
- Neurofilament light level (Cerebral Spinal Fluid (CSF) or serum) (if part of the participant's Standard of Care (SoC)) (if different from baseline data point)
- Relapse Review
- DMT Review
- MDT Summary

Unscheduled Visit

An unscheduled visit is likely to occur if a trial participant is switched to another DMT thereby necessitating a re-baselining MRI**.** If this occurs, then Year 1 (Visit 3) should occur 12 months from this 'unscheduled visit'. The two PROs will be sent remotely to them *via* Castor's ePRO platform.

- Document reason for the visit
- most recent web-EDSS or clinical EDSS (if different from baseline data point)
- 9HPT (if part of the participant's SoC) (if different from baseline data point)
- T25-FW (if part of the participant's SoC) (if different from baseline data point)
- SDMT (if part of the participant's SoC) (if different from baseline data point)
- SST (if part of the participant's SoC) (if different from baseline data point)
- Neurofilament light level (Cerebral Spinal Fluid (CSF) or serum) (if part of the participant's Standard of Care (SoC)) (if different from baseline data point)
- EQ-5D-5L (ePRO)
- Healthcare and Other Resource Use Questionnaire (ePRO)
- DMT Review
- Relapse Review
- MDT Summary

9.4.2 Informed Consent

Details of informed consent may be found in Section 9.1.7. Consent must be obtained by a study doctor or trial nurse (PI or delegate sub-investigator) on the trial's delegation log.

9.4.3 Other information to be captured

Whilst AssistMS will fundamentally focus on follow-up datasets of FLAIR and T2 weighted MRI, some participants will receive Gadolinium-DTPA contrast as per their clinicians' indication. We do not expect a significant difference between the study arms in terms of sensitivity for Gd-enhanced lesions – such lesions are usually clearly discernible by visual inspection. We will capture both administration of Gd-contrast and the presence of Gd-enhanced lesions in the CRF. However, no specific outcome with respect to Gd-enhanced lesions will be obtained as part of AssistMS

We will also capture Year of MS Diagnosis, Age at MS Diagnosis, Current DMT (if applicable), past MRI head (if available and usable for icobrain ms) and demographic information. This information should be captured in source documents. Demographic information will include:

Date of birth
- Sex at birth (M/F)
- Gender
- Year of MS/CIS Diagnosis (disease duration calculated by eCRF)
- Age at MS/CIS Diagnosis (calculated by eCRF)
- Ethnic Group

9.4.4 Inclusion and Exclusion Review

In/exclusion review can be undertaken without the participant being present. PI or delegated sub-investigator/research nurse/trial coordinator should ensure that the screened patient is eligible for the trial. In this study, this should be straightforward by discussion with the potential participant during their SoC visit, medical records check and checking the eConsent platform. This can be a remote visit and should be completed during the screening/baseline visit. Every inclusion and exclusion criteria must clearly and individually be documented in the patients' medical notes whether taken from the eConsent platform or during a face-to-face visit.

9.4.5 Randomisation

Prior to randomising, documentation by the investigator that the clinical records were checked for all inclusion and exclusion criteria is required. The CRF (Screening and eligibility criteria sections) will run through these criteria as well (Sections 7.1, 7.2, 9.2)

9.4.6 Check past head MRI

The 'past MRI head', if available, should be accessed on PACS and, as described in the MRI protocol, identified if suitable for ico**brain ms** by a trial delegated neuro-radiologist.

9.4.7 Correlation of EDSS and other clinical study measures

If web-EDSS, clinical EDSS, 9-HPT, T25FW and SDMT are associated with the retrospective scan and available, this data should be recorded in the patient's medical record during the screening/baseline visit.

9.4.8 Review MRI activity compared to previous MRI assessment (on-site neuroradiologists)

On-site neuro-radiologists will review MRI brain datasets of participants as part of their routine follow up and document their findings using a template provided by the trial team. Datasets will be randomised for assessment with or without ico**brain ms** technology. General parameters we will collect include:

- Date of MRI
- Image/dataset sent to ico**metrix** for AI analysis (ico**brain ms**) (if on interventional arm) (Note on file when image was sent to ico**metrix**)
- MRI (with/without ico**brain ms** report) available for Radiologist review.

- Time from MRI upload to ico**metrix** until return of annotated MRI and ico**brain** report (only for those on interventional arm)

- Time from MRI acquisition to MDT referral

- Lesion count (New and/or expanding)

- Was Gadolinium administered with the scan and, if so, did it indicate enhancement?

- Presence of brain volume loss (Yes/No)

Full details regarding what data will be collected will be provided in an MDT template we will require sites to fill in for each trial participant.

9.4.9 Web or clinical Expanded Disability Status Scale EDSS

The EDSS is a disability scale that ranges in 0.5-point steps from 0 (normal) to 10.0 (death) (J. F. Kurtzke 1983; Kappos et al. 2015; John F. Kurtzke 2015). The full scale can be found in the ChariotMS Assessment Manual. In addition to trial required EDSS assessments, further EDSS assessments for individual patients may be requested between visits (i.e., during an MS relapse, neurological worsening, etc.)

The EDSS is based on a standard neurological examination, incorporating functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and cerebral [or mental]) and ambulation rated and scored as FSS. Each FSS is an ordinal clinical rating scale ranging from 0 to 5 or 6. These ratings are then used in conjunction with observations and information concerning ambulation and use of assistive devices to determine the EDSS score.

9.4.10 9-Hole Peg Test (9-HPT)

The 9-HPT is a quantitative measure of upper extremity (arm and hand) function (Goodkin, Hertsgaard, and Seminary 1988; Feys et al. 2017). The test device consists of a container with nine pegs and a wood or plastic block containing nine empty holes. The patient is to pick up each of the nine pegs one at a time and as quickly as possible, place them in the nine holes. Once all the pegs are in the holes, the patient is to

remove them again one at a time as quickly as possible and replace them into the container.

This assessment will only be recorded if it was done as part of the participant's normal standard of care visit.

9.4.11 Timed 25 Foot Walk (T25FW)

The Timed 25-Foot Walk is a quantitative measure of lower extremity function. It is the first component of the Multiple Sclerosis Functional Composite (MSFC) administered at each visit. The patient is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The task is immediately administered again by having the patient walk back the same distance. Patients may use assistive devices when doing this task. In clinical trials, it is recommended that the treating neurologist select the appropriate assistive device for each patient (MSFC Manual, October 2001).

This assessment will only be recorded if it was done as part of the participant's normal standard of care visit.

9.4.12 Symbol Digit Modality Test (SDMT)/Symbol Substitution Task (SST)

Up to 70% of people with Multiple Sclerosis (MS) experience cognitive problems which can be debilitating and impact on day-to-day life. The SDMT (Smith, n.d.) has demonstrated sensitivity in detecting not only the presence of cognitive impairment but also changes in cognitive functioning over time and in response to treatment. The SDMT is recognized as being particularly sensitive to slowed processing of information, which is commonly seen in MS (Benedict et al. 2018). The SDMT is brief, easy to administer, and involves a simple substitution task that both children and adults can easily perform. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. Responses will be collected verbally, and administration time is approximately 5 minutes. This assessment will only be recorded if it was done as part of the participant's normal standard of care visit.

The Symbol Substitution Task (SST) provides a digital alternative based on the SDMT. The SST was developed as part of a multi-centre project exploring cognitive assessment and rehabilitation in clinical practice (NEuRoMS; www.neuroms.org). Some clinical sites involved in AssistMS also participate in NEuRoMS and are well familiar with the SST.

9.4.13 DMT Review

Documentation of whether or not a new DMT was prescribed at the baseline, M12, unexpected visits or at withdrawal.

9.4.14 Relapse Review

As is standard of care, participants will be evaluated for relapse by the Investigator at each visit throughout the study and, if necessary, at unscheduled visits to confirm relapse occurring between regular visits. All new or worsening neurological events compatible with an MS relapse are to be reported in the appropriate eCRF.

9.4.15 MDT Summary

As described in Section 9.4, a delegated team member will summarise the MDT specifically around the information requested in Sec 9.4 and entered into the participant's medical record as part of the visit.

9.4.16 System Usability Scale

The System Usability Scale (SUS) is a ten-item questionnaire giving a global and subjective assessment of usability originally developed by John Brooke (Brooke 1996).

For this trial, we have adapted this general SUS to comprise questions on the usability of the ico**brain ms** software. The ten questions are scored by means of a Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). The questionnaire will be filled out by the neuro-radiologist at the end of the study to evaluate the ease of use, criticism or likeability of the software. The questionnaire will be completely anonymous and in addition to the ten questions, will leave space for a short paragraph where the radiologists can enter their main criticism or what they liked most about the software.

9.5 Patient Reported Questionnaires

Patient-reported outcome (PRO) data will be collected via questionnaires electronically in this study. The questionnaires will be completed at specified time points. To ensure instrument validity and that data standards meet regulatory requirements, questionnaires will be self-administered electronically.

Whenever possible, the EQ-5D-5L and Healthcare and Other Resource Use questionnaires will be completed as per the schedule of assessment in section 9.7. The EQ-5D-5L Healthcare and Other Resource Use Questionnaire questionnaires will be collected at baseline (month 0), Month 6 and Month 12. Copies of all PRO's can be found in the AssistMS Assessment Manual. Automated reminders will be sent 2 days and 7 days after the original link was sent if necessary.

In the event that the patient is unable to complete PROs on his or her own (e.g., due to problems with eyesight or dexterity) and since these will be administered remotely, a carer may assist, however, they should not influence responses in any way and questions and response options should be read out verbatim.

9.5.1 EuroQoL Eq-5D-5L

The EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen and Szende 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale that measures health state (see AssistMS Assessment Manual). Published weighting systems allow for creation of a single composite score of the patient's health status. It will be used in this study for informing the economic evaluation.

9.5.2 Healthcare and Other Resource Use Questionnaire

The Healthcare and Other Resource Use Questionnaire is a purpose developed questionnaire asking participants to report their use of inpatient, outpatient and community healthcare, social care, help with personal care, out-of-pocket costs related to condition and impact on employment in the previous 6 months. Data collected include: seeing healthcare professionals in the community, in hospitals, admissions, home help/personal care, rehabilitation, home modifications and the impact on work.

9.6 Digital Access Request Service datasets

The following datasets will be requested from NHS England using each participant's relevant PID. This will include their NHS number, DOB, sex and postcode. The PID will be stored in a safe haven server at QMUL for the duration of the study and will come directly from each trial site. At the end of the study, the participant's PID will be sent to the NHS England DAR service which will then extract the data in each data set, correlate that with the trial ID and then send pseudonymised data directly back to the safe haven server. Details for the data flow can be found in Sec 14.2.1

- Hospital Episode Statistics Outpatients (HES OP)
- Diagnostic Imaging Data Set (DID)
- Admitted Patient Care (HES APC)
- Critical Care (HES Critical Care)
- Emergency Care Data Set (ECDS)

Additionally, linkages will also be sought with the Civil Register for deaths and the causes of death. As above, details for the data flow can be found in Section 14.2.1.

9.6.1 Hospital Episode Statistics Outpatients (HES OP)

This report includes but is not limited to analysis of hospital outpatient appointments by patient demographics, diagnoses, attendance type, operations, specialty and provider level analysis. It describes NHS outpatient appointments in England, rather than the number of patients. The purpose of this publication is to inform and support strategic and policy-led processes for the benefit of patient care and may also be of interest to researchers, journalists and members of the public interested in NHS hospital activity in England.

9.6.2 Diagnostic Imaging Data Set (DID)

The Diagnostic Imaging Dataset (DID) is a central collection of detailed information about diagnostic imaging tests carried out on NHS patients, extracted from local Radiology Information Systems (RISs) and submitted monthly.

The DID captures information about referral source and patient type, details of the test (type of test and body site), demographic information such as GP registered practice, patient postcode, ethnicity, gender and date of birth, plus items about waiting times for each diagnostic imaging event, from time of test request through to time of reporting. NHS Digital collects the dataset at patient level. It is reported here in summary form as Official Statistics.

9.6.3 Admitted Patient Care (HES APC)

This report includes but is not limited to analysis of hospital episodes by patient demographics, diagnoses, external causes/injuries, operations, bed days, admission method, time waited, specialty, provider level analysis and Adult Critical Care (ACC). It describes NHS Admitted Patient Care Activity, Adult Critical Care activity and performance in hospitals in England. The purpose of this publication is to inform and support strategic and policy-led processes for the benefit of patient care and may also be of interest to researchers, journalists and members of the public interested in NHS hospital activity in England.

9.6.4 Critical Care (HES Critical Care)

An Intensive Care Unit (ICU) or High Dependency Unit (HDU) ward in a hospital, known as a critical care unit, provides support, monitoring and treatment for critically ill patients requiring constant support and monitoring to maintain function in at least one organ, and often in multiple organs. Medical equipment is used to take the place of patients' organs during their recovery.

The Critical Care Minimum Dataset (CCMDS) is submitted by hospitals to the Secondary Uses Service (SUS). The CCMDS contains 34 data items on periods of care in adult critical care units, of which 14 data items are mandatory for submitters. Each month, record-level data extracts are taken from SUS to populate the Hospital Episode Statistics (HES) data warehouse which is used to produce this publication.

Critical care records contain information on:

- The organ support that the patient received; and
- The method, source and location of admission and discharge.

In addition, data in the associated HES APC records contain further details including:

- Patient demographics, including sex and age; and
- Diagnosis and treatment details.

9.6.5 Emergency Care Dataset (ECDS)

The Emergency Care Data Set (ECDS) collects information about why people attend emergency departments and the treatment they receive to:

- Improve patient care through better and more consistent information
- Allow better planning of healthcare services
- Improve communication between health professionals

9.7 Schedule of Study Interventions (per participant/per visit and MRI related visits)

Table 6: Schedule of Assessments – Clinical

Study Procedures	Visit 1 (Screening and Baseline during SOC visit)	Visit 2 (ePROs only)	Visit 3 (End of trial during SOC visit)[2]	Early Withdrawal[3]	Unscheduled Visit[4]
	(+/-12 weeks to Day 0 from baseline visit to Visit A) (M0 MRI visit)[1]	M6 (+/- 2 weeks)	M12 (+/- 12 weeks)		
Informed Consent	X				
Year of MS Diagnosis, Age at MS Diagnosis, disease duration, MS Subtype (RMS, SPMS, PPMS), Current DMT (if applicable), past MRI head (if available and acceptable for icometrix[5]) and demographic information[6]	X				
Inclusion & Exclusion Review[7]	X				
Randomisation (Individual)	X				
If past MRI head available, check for correlation of EDSS and other clinical study measures [8]	X				
Radiologist check past MRI head (if available and useable-see Neuroradiology visit tab)	*If available (x)*				

Web or Clinical Expanded Disability Status Scale result	X		X	(X)	(X)
Nine-Hole Peg Test (9-HPT) result (only if recorded as part of SoC)[9]	(X)		(X)	(X)	(X)
Timed-25 Foot walk (T25-FW) result (only if recorded as part of SoC)[9]	(X)		(X)	(X)	(X)
Symbol Digit Modality Test (SDMT) and/or Symbol Substitution Task (SST) (only if recorded as part of SoC)[9]	(X)		(X)	(X)	(X)

Table 6: Schedule of Assessments – Clinical (continued)

Neurofilament Light (CSF or Blood serum) result (only if recorded as part of SOC)[9]	(X)		(X)	(X)	(X)
EuroQoL EQ- 5D-5L[10]	X	X	X		X
Health Resource Use Questionnaire [10]	X	X	X		X
Relapse Review	X		X	(X)	X
DMT Review	X		X	(X)	X
MDT Summary[11]	X		X	(X)	X
DARS Datasets[12]			X		

Footnotes:
1). Potential trial participants will be approached once they have both the clinic visit and MRI visit scheduled within 12 weeks of each other. It does not matter what comes first, however, they must be consented before the 'Visit 1' clinic visit and randomised before the MDT where they will be discussed.
2). Exact timing of the final MRI and clinical visit is difficult to approximate. Therefore, we will allow 12 weeks between one or the other.
3). The early withdrawal visit will not have any MRIs associated with it, if an MRI was obtained after the M0 baseline MRI visit then that MRI can be used in the study.
4). An unscheduled visit could arise if, for example, a participant is switched to a new DMT that requires re-baselining. If this occurs, then the M12 visit will occur from this re-baselining.
5). Whether or not there is a retrospective MRI or if is useable by ico**metrix** for analysis, the participant may still enter the trial.
6). Demographics include DOB, Sex at birth, gender, Year of MS Diagnosis, Age at MS Diagnosis, Ethnicity
7). As all IC/ECs can be checked without the participant, this can be confirmed without them being present and therefore done remotely during this Visit.
8). EDSS and any other clinical study measures (9HPT, T25FW, SDMT, NfL) should be noted in the write up of participant's visit.
9). Only results will be collected if done as part of SoC. We will not be administering any tests or taking any blood samples in this study.
10). These PROs will be remotely administered and a reminder to the participants will be sent out 2 days and then 7 days (if required) after the ePRO link was sent.
11). A summary of the MDT results, as described in section 9.4 should be prepared and entered into the participant's notes.
12). DARS datasets will not directly involve the participants. If they give consent for these, the trial sites will provide specific information to DARS and instructions around how to do this will be provided.

Table 7: Schedule of Assessments – Neuroradiology

Study Procedures	**Visit A (MRI Baseline)**	**Visit B (MRI End of trial)[1]**	**Early Withdrawal[2]**	**Unscheduled Visit[3]**
	M0 (+/-12 weeks to Day 0 from baseline visit at Visit 1)	**M12 (+/- 12 weeks)**		
Radiologist check past MRI head for retrospective analysis (if available and acceptable for icobrain ms analysis)	X			
Review MRI activity compared to previous MRI assessment (Neuro-radiologist)	X	X	(X)	(X)

System Usability Scale[4]		X		

Footnotes:
1). Exact timing of the final MRI and clinical visit is difficult to approximate. Therefore, we will allow 12 weeks between one or the other.
2). The early withdrawal visit will not have any MRIs associated with it, however if an MRI was obtained after the M0 baseline MRI visit then that MRI can be used in the study.
3). An unscheduled visit could arise if, for example, a participant is switched to a new DMT that requires re-baselining. If this occurs, then the M12 visit will occur from this re-baselining.
4). The system usability scale is a simple questionnaire for the neuro-radiologist to fill out at the end of the study. This only needs to be done once and not with every participant.

Table 8: Schedule of Assessments – General radiologist subgroup

Study Procedures	**Visit A (MRI Baseline)[1]**	**Visit B (MRI End of trial)**	**Early Withdrawal[2]**	**Unscheduled Visit[3]**
	M0	**M12**		
Pseudonymised MRI accessed by radiologist through the concurrent supervision portal (an icometrix webportal) for analysis (Only specified MRIs)	X	X		(X)
Review MRI activity compared to previous MRI assessment (Only specified MRIs)	X	X	(X)	(X)
System Usability Scale[4]		X		

Footnotes:
1). A subset of MRIs will be randomly chosen for inclusion in this sub-study with general radiologists. They will be asked to report their findings on a CRF directly on the ico**metrix** portal. A defined time window for analysing these MRIs is not applicable for this sub-study.
2). The early withdrawal visit will not have any MRIs associated with it, however if an MRI was obtained after the M0 baseline MRI visit then that MRI can be used in the study.
3). An unscheduled visit could arise if, for example, a participant is switched to a new DMT that requires re-baselining. If this occurs, then the M12 visit will occur from this re-baselining.
4). The system usability scale is a simple questionnaire for the neuro-radiologist to fill out at the end of the study. This only needs to be done once and not with every participant.

9.8 Intervention (icobrain ms)

As described in Sec 16.1

9.9 Data Collection (CRFs) and Storage

As described in Sec 14

9.10 Follow up Procedures

Described above in Sec 9.4.1 and 9.6

9.11 Laboratory Procedures

We will only be collecting data from serum or CSF-Neurofilament light (NfL) samples that are routinely collected by a site as part of SoC. The data will be located in the participants medical record. Therefore, there are no procedures regarding taking any blood, sample prep or chain of custody responsibilities.

9.12 Radiology Assessments

The scans required for processing with ico**brain ms** are the following:

1. **A fast localizer (3-plane)**
- A quick acquisition in sagittal, coronal and transverse plane
- The head should be centred laterally along the interhemispheric fissure and centred on the thalamus for the anterior/posterior and superior/inferior planes (crucial!)
- The images should include cerebellum and C1-C3 in the Field of View (FOV) and anterior/posterior plane should include the nose

2. **3D T1-weighted image**
- Preferably a sagittal acquisition (can be acquired coronally as well)
- Voxel size 1mm x 1mm x 1mm with 0mm spacing / slice gap
- Max slice thickness + slice gap < 1.5mm

3. **T2-weighted FLAIR image**
- 3D FLAIR is preferred (preferably sagittal)
- 2D flair (preferably axial, can be done sagittal as well) - max slice thickness of 3mm and 1mm x 1mm in-plane resolution

ico**metrix** will provide the sites with a questionnaire to determine the scan parameters and protocols per site. Based on the responses, an Image Acquisition Manual will be drafted with scan parameters and suggestions for image protocols and scan quality.

Where possible, the sites will try to acquire all patient scans on a 3 Tesla (3T) scanner. 1.5T scanners with a good protocol (i.e. adhering to the quality requirements as detailed in the Image Acquisition Manual) will also be accepted. The sites will try as much as possible and where possible to have all time-points for one patient taken on the same scanner (field strength and manufacturer / type), to ensure a correct longitudinal assessment. Consistency in scanner, software, and protocol is highly recommended to allow for a reliable comparison of MRI data over time. Sequence parameters, scanner type, and scanner software can have a relevant impact on the visualisation of brain tissue and lesions, making it difficult to distinguish parameter variability from disease progression. Consistent scanning of patients on the same scanner over time is advisable for both visual reading and post-processing.

9.13 Radiology Team Assessments

The teams of radiologists involved in the study will consist of:

1. Experts at sites: Consultant neuro-radiologists with subspecialty training and experience in CNS neuroinflammation, and the MS MDT decision-process, who will work on-site.
2. Non-experts off-site: Three consultant radiologists with no subspecialty expertise in neuro-inflammation or MS. A representative sample size of 1:1 SOC vs SoC + AI participant's MRI datasets will be used for this objective. This sub-team is part of an exploratory objective and will therefore not impact any of the other outcomes.

MRI visual assessment will be performed according to a minimal structured set of indices measurements in order to allow quantitative comparison with the ico**brain ms** report. The indices used in the report were informed by the results of the Barts Health AssistMS MRI audit and prior knowledge (Alessandrino et al. 2018) to ensure that the visual assessment report will not deviate from the current standard of care.

Since the radiologists will alternate the standard and ico**brain ms**-assisted assessment, we will also evaluate the potential impact of the use of ico**brain ms** on the standard visual report by retrospective analysis of visual radiological reports.

To provide similar conditions for MRI reviews, Non-Experts off-site will (i) work independently and (ii) be given the same time constraints (imposed by clinical practise) as for Experts on-site.

9.13.1 General Radiology Review

Three general radiologists without specific training or expertise in neuroradiology and/or MS will be identified. 100 MRI images (1:1 SOC: intervention) will be analysed by three radiologists which will then be analysed to examine the variability in ratings. This will then form the basis of the final sample size determination for this exploratory outcome. These 100 images will be sent to the general radiologists through the 'concurrent supervision portal' (a webportal managed by ico**metrix**). The pseudonymised images are made available on this portal and can be accessed by the radiologists via a weblink. Via this portal they will be able to assess the images either with or without help of ico**brain ms**, depending on the randomisation of any particular participant. After radiological analysis, a template is available, via the same portal, to determine the lesion load (new and/or expanding).

- Radiologist: Review MRI new lesions compared to previous MRI assessment
- System Usability Scale (only once at Month 12)

9.14 Participant withdrawal

Participants may be withdrawn from the trial for any of the following reasons:

- At the request of the participant
- Inability or failure of the participant to comply with the protocol requirements, including nonattendance at study visits and loss to follow-up.
- Other reason at PI's discretion
- Termination of the study by the Sponsor.

The site PI may decide to withdraw a participant from study treatment at any time if intercurrent illness or other medical condition suggests that continued participation would not be in the best interests of the participant. In this case the participant should continue with other aspects of the trial, including follow-up assessments, unless withdrawal from all aspects of the trial is judged by the PI to be in the participant's best interests. Participants who are withdrawn for clinical reasons will be referred to an appropriate clinical team for follow-up as part of their standard of care.

Participants who withdraw or are withdrawn early will undergo the early termination visit procedures as summarised in the Schedule of events in Section 9.5 and in Section 9.4 above. The reasons for withdrawal where known will be documented in the source documents and eCRF.

Participants will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. If a participant asks to be withdrawn, where possible the PI will seek clarification on whether the participant wishes to withdraw from all aspects of the trial (including follow-up assessments) or only from the intervention.

In the event a participant loses capacity to make medical decisions, post informed consent, the participants next of kin/power of attorney should decide in the best interest of the participant whether to continue taking part in the trial or withdraw.
If a participant is withdrawn from all aspects of the trial, any data collected to date will still inform the intention-to-treat (ITT) analysis; participants will be informed of this during the consent process. Once withdrawn from the trial, participants will not be able to re-enter.

9.15 End of study definition

End of Trial (EoT) is defined as the date of Last Participant Last Visit MDT (LPLV MDT). Due to the nature of the trial, this will either be when the LPLV is at their final M12 MRI or their M12 clinical visit, whichever event occurs last. However, as any patient discussion and treatment decisions will be decided at their MDT and need to capture this data, this is the End of Trial.

10. Assessment and management of risk

Ico**brain ms** is a medical device intended for automatic labelling, visualisation and volumetric quantification of segmentable brain structures from a set of MR images. The software is intended to automate the current manual process of identifying, labelling and quantifying the volume of segmentable brain structures identified on MR images. Hence, the device itself has no direct impact on the patient. In support of a validated radiological report, it may contribute advice by the care team on DMT decisions.

Ico**metrix** ensures risks are properly followed up using SOPs:

- Vigilance and incident reporting (UK) in case of issues with the device: this procedure describes the necessary action to take in case of severe incidents due to product quality or safety related problems with the output to protect the users and patients, respecting the regulatory and statutory requirements. Also include requirements regarding recalls or Field Safety Corrective Actions.
    - Related to this are the following procedures:
        - Customer feedback and complaint handling
        - Non-conformity procedure
        - Post-market surveillance
        - Field safety notice (FSN) form, FSN customer reply form, FSN distributor/importer form
        - Corrective And Preventive Actions (CAPA) management procedures
        - Security incident response & recovery
        - Data breach management
- Risk Management: procedure which describes the risk management process of the medical device, from the identification of hazards associated with it, to the estimation and evaluation of the associated risks, to the control of these risks, and to the monitoring of the effectiveness of those control measures. The risk management process is applied throughout the whole lifecycle of the medical device.
    - Related to this are the following procedures:
        - Risk Management Plan, Risk Management Matrix, Risk Management Report, Risk Policy, Risk Safety Characteristics
        - Usability Engineering File
        - Customer feedback and complaint handling
        - Post-Market Surveillance; this process allows to actively and systematically gather, record and analyse relevant data on the quality, performance and safety of a device throughout its entire lifetime, and to draw the necessary conclusions and to determine, implement and monitor any preventive and corrective actions
        - Design & Development procedure
        - Clinical evaluation
        - Release procedure

For this CIP, we will use the following documents to guide the trial: (1) the vigilance and incident reporting UK SOP, (2) the risk management SOP, (3) the risk management plan SOP, (4) risk management matrix SOP, (5) risk policy SOP, and (6) the post-market surveillance SOP. All will have AssistMS work instructions associated with each SOP to ensure the trial meets its reporting obligations and duplicate reporting to regulatory agencies (if warranted) does not occur.

With regards to risk around other procedures that will be used (Sec 9.4-9.5), all are either part of a patient's SoC or use of a PRO (ie EQ-5D-5L). As the trial's arms are SOC:AI + SOC, there will always be expert neuro-radiologists involved with every scan interpretation. Furthermore, as no CTIMPS or biological samples are involved with this study, apart from those taken as a participant's SOC, there are no significant further risks associated with the study.

There will also be CRA trial monitoring (both site visits and remote monitoring) to ensure risks are correctly managed and addressed.

Additionally, as part of the TMG duties, a summary of any medical device incidents will be maintained and as part of the yearly Annual Progress Report (Sec 12.1), reported to the HRA/REC as well as the TSC.

11. Statistical considerations

The primary analysis will be conducted on an ITT basis. If there are a substantial number of participants who did not receive their allocated intervention, a secondary per-protocol analysis will also be conducted, including only participants whose MRI was assessed according to their allocated group.

11.1 Sample size

The primary endpoint will be the proportion of participants with MRI detected disease activity, as reported by the radiologist assessment with/without support of ico**brain ms**. In order to have 80% power to detect an 8% increase in the proportion with MRI detected disease activity when using standard of care compared to ico**brain ms** (40% vs 48%), 668 patients are needed per arm with 10% drop-out (1336 patients in total).

The proportion with MRI disease activity with standard care is 40%. The effect size is based on a previous study that found that use of ico**brain ms** increased the proportion with disease activity by 8% (Daugherty et al. 2005; Río et al. 2012; Sá, de Sá, and Sousa 2014b). It is assumed 10% of participants will drop out before data collection is completed, based on the drop-out commonly seen in similar studies (H. N. Beadnall et al. 2019b; Jain et al. 2015a; D. Sima et al. 2020; H. Beadnall and Billiet 2017).

11.2 Method of analysis

A detailed statistical analysis plan (SAP) will be produced prior to analysis and agreed by the Trial Steering Committee (TSC). The SAP will detail the statistical methods used for description of demographic and baseline characteristics, assessment of adherence to protocol radiological assessment, evaluation of impact of ico**brain ms** on primary, secondary and exploratory outcomes.

11.2.1 Analysis population and missing data

The statistical analysis will be based on all participants as randomised, including all patients where possible according to the intervention to which they were randomised, irrespective of whether the ico**brain ms** intervention was used for the assessment of their MRI scan or not (intention to treat analysis).

If there is substantial deviation from the planned randomisation schedule, a secondary per-protocol analysis will be considered, which will include only individuals who had the intervention to which they were assigned as specified.

Missing data will be identified, and an effort made to return to the original medical records to obtain the data. Total number of patients withdrawing and reasons for withdrawal will be tabulated by the treatment group. The characteristics of the patients with missing data will be compared to those with complete data and patterns compared between the treatment groups. In the event of substantial differences in withdrawal patterns being found, further sensitivity analyses will be carried out to investigate the robustness of the results.

11.2.2 Description of the cohort

A CONSORT diagram will be used to describe the course of patients through the trial. Baseline characteristics will be summarised by randomised group. Numerical variables will be summarised using summary statistics (mean, standard deviation, median, minimum, and maximum) by allocated group, and categorical variables will be presented using frequency distributions by allocated group.

11.2.3 Statistic methods – outcomes

Primary outcome

The primary analysis will be a comparison of the odds of disease activity being reported on the radiologist assessment of the MRI scan between the ico**brain ms** and standard of care arms. Odds ratios and 95% confidence intervals will be calculated using a logistic generalised estimated equations (GEE) model with robust standard errors to account for repeated MRI scans on the same participant. The inclusion of additional scans for some participants will increase the power to detect an impact of ico**brain ms** on detection of disease activity. The analysis will adjust for the randomisation stratification variables. Any additional covariates will be prespecified in the SAP.

Secondary outcomes

Binary outcomes will be compared between treatment groups using logistic regression adjusting for the randomisation stratification variables. The mean difference in continuous patient-reported outcomes will be compared between groups using linear regression, adjusting for the baseline value and randomisation stratification variables. Where appropriate, a generalised estimated equations (GEE) model with robust standard errors will be used to account for repeated measures on the same participant. Negative binomial regression will be used to compare relapse rate between the treatment groups adjusted for the randomisation stratification variables. Any additional covariates will be prespecified in the SAP.

If parametric assumptions for any of the regression models are substantially violated, bias corrected and accelerated bootstrap confidence intervals will be used for inference.

Tertiary outcome

A tertiary outcome of AssistMS is to conduct a subgroup analysis to assess whether the impact of ico**brain ms** on treatment initiation or switch decisions differs between patients with or without clinical deterioration. To do this a logistic regression will be used with the outcome being treatment initiation or switch and an interaction included between the arm (interventional and SoC) and whether the patient had recent clinical deterioration at the time of the radiological assessment. A generalised estimated equations (GEE) model with robust standard errors will be used to account for repeated assessments on the same patient. The model will adjust for the

randomisation stratification variables. Any additional covariates will be prespecified in the SAP.

Exploratory outcomes

An exploratory objective of AssistMS is to assess the impact of ico**brain ms** on the level of agreement between neuro-radiologists and general radiologists. Krippendorff's Alpha will be calculated for the level of agreement on whether the MRI scans show disease activity (Yes/No) between neuroradiologists and general radiologists separately for the patients with SOC assessment and patients assessed with the assistance of ico**brain ms**. The ratio of Krippendorff's Alpha for SOC versus ico**brain ms** will be calculated along with bootstrap 95% confidence intervals to quantify the difference in level of agreement between trial arms.

A second exploratory objective is to assess the contribution of MRI change in decision making. The proportion of patients with treatment initiation or switch decisions will be compared between those with and without MRI change (lesions and atrophy) in a subgroup analysis by arm. To do this logistic regression will be used with the outcome being treatment initiation or switch and including as predictors presence of MRI change (yes/no) on the scan at the visit prior to treatment decision making, arm (intervention/SoC) and an interaction between MRI change and arm. Generalised estimated equations (GEE) model with robust standard errors will be used to account for repeated assessments on the same patient. The model will adjust for the randomisation stratification variables. Any additional covariates will be prespecified in the SAP.

11.3 Health Economic analyses

The primary outcome for health economic evaluation will be the incremental cost per QALY gained with AI-assistance vs usual care from the perspective of NHS and personal social services perspective and, separately, from the societal perspective. We will also conduct within-trial cost-consequences analysis.

Health economic analysis will include two components:

1. Within-trial cost-consequences analysis of participant health care and other costs and quality of life (QOL) outcomes, including hospital resource impact.
2. A lifetime evaluation of the incremental cost-effectiveness of implementing ico**brain ms** into the routine care of pwMS using a microsimulation model projecting over a lifetime horizon health care and other costs, health-related quality of life adjusted survival with and without use of AI assistance technology for MRI review.

To support health economic analyses the following information will be collected:

- Participant QoL as measured by the EQ-5D-5L instrument administered at baseline, 6 and 12 months of follow-up in the study
- Radiologist MRI review reporting times for randomised participants to estimate the impact of use of AI assistance technology on the radiological workflow
- Linked hospital care administrative datasets for diagnostic imaging, outpatient, inpatient, critical and emergency care from 6 months prior to entry into the study to the end of follow-up in the study
- Participant healthcare including community and primary care, social care, private resource use and impact on employment using patient resources use questionnaires administered at baseline, 6 and 12 months of follow-up in the study.

In the within-trial economic analysis we will assess the impact of allocation to ico**brain ms** assisted radiologist assessment on QoL, measured using EQ-5D utility at 6- and 12-months follow-up, and impact on **health and social care and other resources during study follow-up.**

Lifetime microsimulation modelling will be undertaken for the RRMS and SPMS populations and may be considered for those with CIS and PPMS depending on available external data on disease course in people with these conditions. Parameterisation of the microsimulation will incorporate evidence generated by the clinical trial, including decisions to initiate or change DMTs, alongside evidence from currently available literature on natural progression of disease and the impact of disease-modifying therapies. We will report incremental cost-effectiveness ratios and net monetary benefit for willingness-to-pay threshold from £0 to £30,000 per QALY gained with AI-assistance vs usual care.

12. Ethics

ico**brain ms** does not directly impact a trial participant and is only an enhancement to the MRI image (as an enhanced colour coded image and bespoke report). All visits will take place as part of SoC clinical or MRI visits, apart from a one-time remote visit where participants will be sent a validated PRO (EQ-5D-5L). Additionally, all participants regardless of trial arm will have their MRIs analysed as per each Trust's SoC procedures, albeit 50% will have ico**brain ms** as well. Therefore, there is little ethical concern for the potential for missing key information. or affecting a trial participant's care.

Before the start of the trial, approval will be sought from the Health Research Authority (HRA) / Research Ethics Committee (REC) for the trial protocol, PIS/IC and other relevant documents e.g. advertisements and HCP information letters. A specific REC specialising in medical device studies will be requested to review this study.

The decision whether an amendment constitutes a minor or substantial amendment lies with the sponsor. Substantial amendments that require review by the Sponsor (and ico**metrix**) (as required by the QMUL/ico**metrix** collaboration agreement) and HRA/REC will not be implemented until the HRA/REC grants a favourable opinion for the study (note that amendments may also need to be reviewed and accepted by NHS Research and Development (R&D) departments before they can be implemented in practice at sites).

All correspondence with the Sponsor, HRA and REC will be retained in the Trial Master File (TMF) at the lead site and Investigator Site File (ISF) at each site. The Chief Investigator will notify the HRA, REC and Sponsor of the end of the study.

12.1 Annual Safety Reporting

Annual Progress Report (APR)

The APR will be written by the CI (using the HRA template) and submitted to the sponsor for review and approval prior to submission to the REC. The APR is due within 30 days of the anniversary date of the "favourable opinion" letter from the REC.

13. Public Involvement

Patientsinresearch.bartshealth@nhs.net
www.jrmo.org.uk/performing-research/involving-patients-in-research/

AssistMS is to a significant degree a response to pwMS keen to access optimum care, particularly effective DMTs. Over many years, BartsMS, an academic group working within the Blizard Institute at QMUL, have educated pwMS and the public through our blog including these general posts about MRI What is MRI – The MS-Blog (multiple-sclerosis-research.org) https://multiple-sclerosis-research.org/2021/12/education-whats-an-mri/

The interaction with pwMS through our blog has been a major driver in our quest to translate new insights in technology and clinical trials into the day-to-day care of pwMS. pwMS diagnosed today regularly tap into online resources and quickly become experts in their condition. This expertise includes the understanding that effective DMT requires regular and reliable MRI monitoring to prevent clinically silent disease activity impacting on their long-term prognosis. Thus, from the outset, the AssistMS team has been driven by the views of pwMS. We have also reached out to the MS Society for their views on AssistMS, and their response and support has been enthusiastic. The team developing AssistMS largely did so in response to pwMS keen to understand their disease and how to manage it, and we will continue to do so.

Patient and Public involvement (PPI) ensures an active partnership between members of the public, preferably someone within the researched disease population, and researchers. The representative will work alongside the research team and will actively contribute to the research process. As the representative is someone living with MS, they will provide useful insights into what it is like to live with the illness, and to be a user of a treatment or health service. This will ensure a higher relevance of the research, accustomed to the needs of patients, carers and service users.

The PPI lead on this study, Dominic Shadbolt, is an expert patient who set up his own YouTube MS based channel and now leads on his own MS Guide website (https://www.youtube.com/@theMSguide). The PPI lead's presence and position within the AssistMS team are testimony to the INVOLVE values the team subscribes to (respect, support, transparency, responsiveness, fairness of opportunity, accountability), and that in AssistMS PPI is a dialogue between researchers and the public, with mutual learnings, rather than a tick box exercise. ico**metrix** have their own history of PPI, particularly in the context of their mobile app solution, ico**mpanion** (not used in AssistMS). The PPI lead will attend regular Trial Management Committee (TMC) meetings with PPI as a fixed item on the agenda. They will help develop the

study protocol and, with support from the team and MS Society, organise meetings with participants and other fellow pwMS to discuss the study at all stages, being mindful to gather equitable and diverse input. The PPI lead will also be key for translating results. Impact assessments of PPI in AssistMS will include an analysis of TMC minutes ("Did PPI alter the course of the study?") and feedback questionnaires from PPI activities.

14. Data handling and record keeping

14.1 Data management

The data collection, storage and handling will be coordinated by the Study sponsor.

ico**metrix** as a company is ISO 27001 certified for information security management, and compliant with 21 CFR Part 11, HIPAA, and GDPR. ico**metrix** will allow data transfer of MRI DICOM images by a secure transfer method, namely the ico**bridge** solution.

All MRI DICOM data will be pseudonymised prior to leaving the hospital. Additionally, file transfer through ico**bridge** uses industry-standard Transport Layer Security (TLS) encryption to ensure secure transfer of data.

The collected data will be uploaded to the secure ico**metrix** cloud in Ireland. The backup location is in Frankfurt, Germany. For the resulting central, harmonised, de-identified database, the necessary access policy and rights will be put in place. As a main principle, each party contributing data will be able to access their own data and the parties in charge of data analysis will have access to the data that is subject of that analysis. ico**metrix** is ISO27001-certified for information security and complies with the General Data Protection Regulation and the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Castor EDC will be the data system for the trial's various data streams except for DARS based data. Castor is compliant with ISO standards (ISO/IEC ISO 27001, ISO 27001/ IEC 27001 NEN 7510/ISO 9001 certified.) CRF's will be designed by the trial team on paper and then transferred to Castor EDC for eCRF development. When complete, the trial team will run a UAT prior to going LIVE with the study. Data management will be undertaken by Castor EDC. In addition to the eCRF, Castor will develop our participant randomisation site, an e-consent platform and an ePRO platform for the trial. Standard operating procedures will be in place for the collection and handling of data received by Castor. All study data will be entered into a database by appropriately trained staff with restricted access. Data collected on the data collection forms will be stored in an electronic database in which the participant will be identified by a unique trial number. The database validity and quality can be ensured and monitored by validation and audit trails.

All data will reside on their cloud (located in London, UK) until the end of the study when it is sent to QMUL's safe haven for analysis and archiving.

Electronic storage is on a restricted area of a file server. The server is in a secure location and access is restricted to a few named individuals.
Data will be processed on a workstation by authorised staff. The workstations access the network via a login name and password (changed regularly). No data is stored on individual workstations. Database data is stored on secure servers and has validated procedures in place to ensure data security, back-up and disaster recovery.

The [Castor] encryption module allows the secure storage of personal data of study participants such as date of birth, name, etc although we will only use trial numbers to correlate a trial participant with their data.
This module allows individual Castor fields (study variables) to be stored in an encrypted manner. This means that the data is stored in the database in the form of a random code. To view the data that lies behind this code, the user needs to have an encryption/decryption key. By encrypting fields and through the dedicated 'Encrypt' user right, you can restrict user access to fields that contain personal data.

DARS data will be obtained by each trial site sending the relevant PID and trial ID directly to the QMUL safe haven for storage until it is sent to NHS England (DARS) at the end of the study for the required datasets. DARS will then send back the requested information. They will use identifiers to link study ID to HES data and, similarly, the QMUL safe haven server will correlate all trial data with trial IDs in preparation for analysis.

The Chief Investigator will ensure that this information is kept confidential. All documents will be stored securely and kept in strict confidence in compliance with the GDPR and Data Protection Act 2018.

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

14.2 Source data

Source data is defined by ICH GCP section 1.51, as "all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

Source documents are defined as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)." [ICH E6 1.52]. Source documents will likely contain participant identifiable data and therefore will be stored securely at investigative sites and will not leave Trust premises. All documents will be stored safely in confidential conditions.

Most data in this study will come from a trial participant's medical record as a part of the standard clinical or MRI visit and thus the medical record will be the primary source document in this study. The only exception to this will be NfL values (contained in a lab report) and any PROs as these will be captured electronically. Any study-specific source document worksheets and study-specific assessment and test documents will be provided to participants by the AssistMS team via the ePRO platform. Data will be entered into the electronic case report form (eCRF) by delegated members of the study team (paper CRFs will be used as a backup ONLY if required and when instructed by the AssistMS team). All interactions around the study with participants will be documented on their medical record (including telephone conversations and emails). Questionnaires (such as EQ-5D-5L and Resource Use Questionnaire) will be completed by participants and every questionnaire should be electronically dated and signed by the person completing it as will be *via* Castor ePRO. The PI/delegate will keep records of all participants (sufficient information to link records e.g., CRFs and hospital records). Further detail on data management may be found in the study data management manual.

Source documents will likely contain personally identifying data and therefore will be stored securely at investigative sites and will not leave Trust premises. All documents will be stored safely in confidential conditions.

Sites that use electronic source (e-source) data should ensure to provide access to e-source systems and database(s) to the AssistMS monitor (and all other authorised personnel at onsite visits). Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. It is the site's responsibility to maintain these e-source databases, to ensure that they are GCP and HRA guidelines compliant and provide a suitable audit trial, and that systems are in place to demonstrate that

the PI at site has clinical oversight of e-source data. Printouts from e-source data must be documented to be verified copies, dated and signed.

14.2.1 NHS England DARS data

As discussed in Section 9.6, DARS data will include NHS number, DOB, sex and postcode. The PID will be stored in a safe haven server at QMUL for the duration of the study and will come directly from each trial site. At the end of the study, the participant's PID will be sent to the NHS England DAR service which will then extract the data in each data set, correlate that with the trial ID and then send data directly back to the safe haven server.

Consent will be sought from participants to access their patient-level routinely collected data captured by the various UK data warehouses, including diagnostic and procedural codes relevant to hospitalisations and/or outpatient attendances for participants treated in NHS hospitals in order to provide a measure of long-term outcomes and NHS resource use.

Linkages will be sought with the NHS England datasets including admitted patient care (HES APC), emergency care (ECDS), outpatient care (HES OP), critical care (HES Critical care) and the Diagnostic Imaging (DID) datasets within the Hospital Episode Statistics (HES) database. Additionally, linkages will also be sought with the Civil Register for deaths and the causes of death. Civil Registration (deaths) provides a complete register of date and cause of death in England and Wales and is administered by NHS Digital.

For the purposes of the data analyses, the research team will only process linked, de-identified data. In order that this dataset can be created, identifiable data will be provided to a QMUL safe haven server for the purpose of the linkage at the end of the study. Each trial site will send this information in an encrypted manner containing participant health service number, date of birth, sex and postcode as well as the unique AssistMS trial identifier for linkage. The trusted third parties will link the cohort to the relevant administrative databases and return the relevant variables.

Identifiable data from each site cohort will be provided to NHS Digital (DARS) for data linkage. Queen Mary University of London will send the health service number, date of birth, sex and postcode as well as a unique patient identifier (de-identified) for linkage. The legal basis for Queen Mary University of London to collect and transfer these personal data to the trusted third parties is participant consent section 261.2(c) of the Health and Social Care Act 2012.

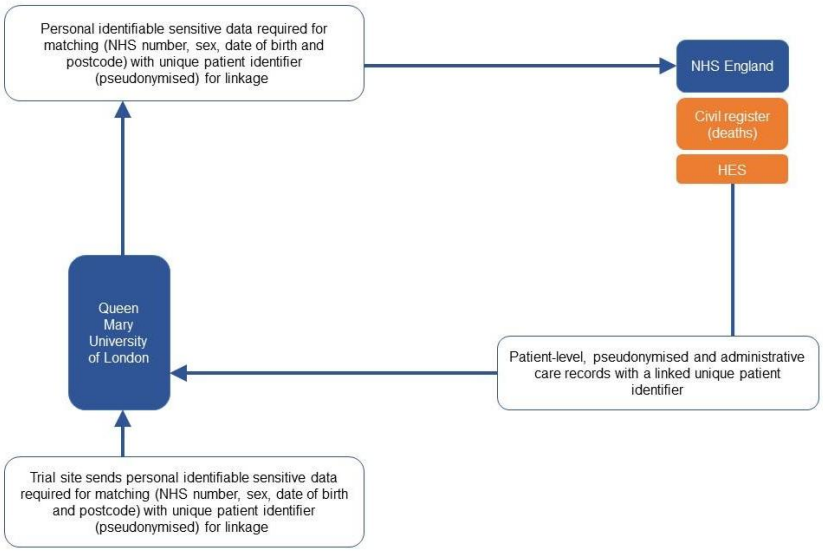


Figure 2: Data flow diagram for DARS

NHS Digital will link Civil Registration (deaths) date and cause of death and HES data with the unique identifier. NHS Digital will link HES data with the unique trial identifier. Queen Mary University of London will receive from NHS Digital patient-level de-identified data only, i.e. HES data with the unique patient identifier. The legal basis for Queen Mary University of London to receive and process data from NHS Digital is Articles 6 and 9 of the General Data Protection Regulations (GDPR).

Queen Mary University of London will aggregate these datasets for each participant using the unique patient identifier (de-identified) to create a research dataset for the processing purposes described within the statistical analyses and health economics analyses contained within the protocol.

14.2.2 High-level description of MRI data source

(Ico**brain ms**) Longitudinal clinical routine data from patients with MS will be provided by the different clinical partners. This data will be available from clinical data collection tools and/or hospital source systems (including electronic medical records (EMR) and picture archiving and communication systems (PACS)). Pseudonymised data will be sent via secure transfer systems (i.e. the ico**bridge** solution), de-identified and structured according to a common data structure and stored in the central repository.

14.2.3 Overview of collected variables on MRI and trial data

Quantitative assessments will be performed on the subclinical imaging data and be added to the database. In the table below, we provide a high-level overview of the Categories of selected data and variables (table 6).

Table 9: Categories of selected data and variables

Collected by the sites	**Collected in the icometrix cloud**	**Collected for DARS requests (direct from trial sites to QMUL safe haven server)**
<u>Patient-specific data:</u> - Demographics	- Pseudonymised MRI DICOM - Year of Birth (YOB) - Gender	- NHS Number - Date of Birth (DOB) - Sex - Postcode
<u>Disease-specific data:</u> - Disease history - Disease status - Relapses - EDSS or web-EDSS - 9-HPT (only if collected as SOC) - T25FW (only if collected as SOC) - SDMT/SST (only if collected as SOC) - serum or CSF-NfL (only if collected as SOC)		
<u>Subclinical data:</u> - MRI from brain and Spinal Cord (SC) - MRI processing/neuroradiologist report - Time to Report		
<u>Treatment data:</u> - DMT - Non-pharmaceutical treatment (NPT) - MDT report		
<u>Patient reported data:</u> - Demographics - Treatment information - PROs (Questionnaires)		

14.3 Case Report Form

The trial data will be captured electronically in a bespoke eCRF and database system. The system will be designed and developed by Castor in accordance with its own SOPs and the Sponsor's SOP 38c "Clinical Research Data Management systems for Interventional and Research Studies", with input from the CI and study team.

A database specification and data management plan will be written and agreed in conjunction with the development of the database to ensure only data required in the protocol is captured in the CRF. The data management plan will also cover all aspects of managing the data such as, the CRF design, the data management systems, data entry, data checking, secure integration of MRI data, query management and cleaning, data transfer, quality control procedures, data extractions, database freeze and lock. Once built, the database will undergo validation including user acceptance testing. Once testing has been completed and the system has been approved, a test report will be documented. The database will be hosted on a secure server hosted by Castor and secure backups of the trial data will also be maintained.

Access to the database will be by password-protected user accounts to prevent unauthorised access. The CI will have overall responsibility for the data stored within the database. Data will be entered into the eCRF by delegated study team members. Further detail on data management may be found in the study data management manual.

CRFs will be pseudonymised using a participant code allocated at time of recruitment. This code will consist of the trial site letters followed by the consecutive recruitment number starting at 001; for example, Royal London Hospital (RLH), participant number 1 (001): RLH-001.

14.4 CRFs as Source Documents

The CRF can at no point act as source documents for this study. Template, paper copies of the CRF are provided to sites for storing ONLY in the Investigator Site File and are provided as a reference to the electronic Case report forms in the bespoke data management systems. These paper case report forms should NOT be used to collect or record source data.

14.5 Confidentiality

The PI has a responsibility to ensure that participant anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study participants will be kept confidential and managed in accordance with the GDPR and Data Protection Act 2018, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval. All trial data will be stored in line with the Medicines for Human Use (Clinical Trials), all subsequent amendments and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) and all subsequent amendments as defined in the JRMO SOP 20 Archiving.

The Chief Investigator and the study team will adhere to these parameters to ensure that the Participant's identity is protected at every stage of their participation within the study. To ensure this is done accordingly, at time of consent each participant will be allocated a unique trial number by either the PI or a member of the study team before undergoing any screening/baseline procedures. As the inclusion and exclusion criteria can be determined before a patient even needs to be approached and there are no screening tests required to potentially eliminate someone, there is no need for separate screening and study ID assignment numbers. The study number will be used on all study documents, apart from source documents which will contain identifying information such as name and NHS number. The minimum identifying dataset will be collected, i.e. only what is necessary for the safe and effective management of the participant's care within the trial, and for analysis of study endpoints. No identifying information will be shared outside the immediate study and clinical team. The only exception for this is for the DARS datasets and the required PID will not be part of the eCRF Castor database.

This means that participant names or any other PID are not included in datasets that are transmitted to any sponsor's or third party's location. Participant medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law. The sponsor, including affiliates, collaborators and licensees may use study data labelled with the participant identification (ID) numbers. Study data may also be shared with independent researchers or government agencies, but only after personal information that can identify the patient has been removed. Participant's study data may be combined with other participant's data and/or linked to other data collected from the participants. Participant's study data may be used to help better understand why people get diseases, how to best prevent, diagnose and treat diseases, and to develop and deliver access to new medicines, medical devices, and healthcare solutions to advance patient care.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, marketing authorization holder monitors, representatives, and collaborators, and the HRA/REC.

Ownership of the data and use of the study results have been described and agreed in the AssistMS project contracts (Grant and Consortium Agreements). In short, the consortium will ensure that dissemination and publication of results will be compatible with the protection of Intellectual Property Rights (IPR), confidentiality obligations and the legitimate interest of the owner(s) of the results.

A repository for the data, meeting European and national criteria for data security, personal data protection and confidentiality, will be prepared and curated by the consortium. The necessary Information Technology (IT) infrastructure and access controls will be implemented to provide all clinical partners standard access to their own data.

14.6 Data Custodian Details

The CI is the Custodian of the research data. Among identifiable data that will be collected and recorded within the source documents are: name, medical record number, NHS number, date of birth, telephone number, address and/or postcode and diagnosis. Only the immediate research and clinical care teams will have access to the source data; however, representatives of the Sponsor and/or regulatory authorities may be granted access to source data for the purposes of quality assurance, audit or inspection, with participants' consent.

Participants will be allocated a unique study number which will be used on CRFs and other documents which are shared with the Sponsor, IDMC, statistician, and other parties where appropriate. See Section 14.7 below for further details. The data will be entered onto a secure computer database, either by trials unit staff or directly via a secure internet connection. All personal information obtained for the trial will be held securely and treated as strictly confidential.

No identifiable information will be used in publication or presentation of the study data. Only anonymised data will be used in presentations and publications. All research data will be kept for 25 years.

14.7 Pseudonymisation

Locally, participants will be identified by their NHS and hospital number. For screening and baseline, the participant's initials (the first letter of their first name and the first letter of their last name) will be used as a means of pseudonymisation parameters. Once the participant has completed screening procedures and is enrolled on to the study, the participant will be allocated a unique study reference number from the enrolment log. The unique study reference number can only be decoded at the local trial site hospital.

All data will be pseudonymised using a unique identifier before it is used or transferred to the site. A consent form for each participant will be identified on the Castor eConsent platform and this information recorded locally at the recruitment site. We will collect the participant's age from their date of birth.

The study number will be a unique identifier composed of the trial site letters and a series of consecutive numbers, e.g. the first enrolled subject may be allocated the subject number 001, the second subject enrolled, subject 002, etc. Thus, all study documents (apart from those source documents which by default contain identifying data, such as hospital medical notes, laboratory results, etc.), including the case report forms and study database will be labelled with subject study number; e.g. RLH-001.

This unique study identifier will be assigned by the PI/delegate once the participant is enrolled in the study. This information will be kept in an enrolment log, which will be kept updated throughout the study, and will be stored in the investigator site file (ISF) with access limited to members of the study team and authorised individuals. The unique study identifier will be used to randomise the participant into a treatment group using the study online randomisation system hosted by Castor. All data will be anonymised before it is used or sent/transferred from the site. Only the study number will be used.

14.8 Access to Data, Source Data and Documents

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

14.9 Record Retention and Archiving

Each site is responsible for record retention and archiving of their own data including both project data and records according to ICH-GCP. Removal of data should be discussed with the study sponsor (QMUL). ico**metrix** will maintain the central data repository of MRI information.

Site files from other sites must be archived for 25 years at the originating site and cannot be stored or archived by the sponsor. Such archiving is only permitted once close out visits have been performed and all actions completed. Permission to archive will be given to sites in writing by the trial manager once permission has been given by the sponsor. The data collected over the trial period will be kept in the secure online solution called Arkivum, managed by the Queen Mary SMD Safehaven.

During the course of research, all records are the responsibility of the Principal (site) Chief (coordination) Investigator and must be kept in secure conditions. Once all sites have been closed and documentation archived, it is a requirement of the Sponsor Policy that the records are kept for a further 25 years. Archiving of CI and Coordinating documentation will be authorised by the sponsor following the submission and publication of the end of study report.

The data collected over the trial time period will be kept in the secure online data management within Castor EDC. Destruction of essential documents will require written authorisation from the Sponsor.

14.9.1 Retention of records by icometrix

Records and documents pertaining to the conduct of this study must be retained by ico**metrix** for at least 25 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

At the end of the study, ico**metrix** will retain an anonymised copy of the participant's MRI's for further research. This data can be used for a post-hoc analysis (e.g. a reader study to compare radiologists with different levels of expertise), for internal software development, etc. To maintain this fully anonymised copy, an independent database is generated which removes all patient information and defaces the MRI images. Further details will be in the Data Management manual for AssistMS.

15. Laboratories

Neurofilament light (Blood serum or CSF NfL) data will be entered in the study's CRF ONLY if part of a trial site patient's SOC. Although discrete lab samples will not be collected in this study, the data from Neurofilament light (serum or CSF) from routine samples will be collected for each trial participant when available.

15.1 Central and local laboratories

As we will not be collecting our own samples for the study but only using the relevant site's data, we will not be responsible for a sample's chain of custody or storage conditions. Relevant SOPs that a site uses for these NfL samples will be available as part of the relevant ISF and TMF.

15.2 Sample collection and preparation

Not applicable

15.3 Laboratory procedures

Will collect lab procedures for sites that routinely collect NfL (Serum or CSF) for reference in the ISF and TMF.

15.4 Sample storage and transfer

Not applicable

16. Interventions and tools

16.1 Devices

Digital solution: ico**brain ms**

ico**brain ms,** with legal manufacturer ico**metrix,** is a cloud-based AI software solution for brain MRI analysis in MS that supports the objective tracking of disease progression in patients with MS. The main components of ico**brain ms** are brain tissue segmentation and MS lesion segmentation on single-time point T1-weighted and Fluid-attenuated inversion recovery (FLAIR) scans, as well as specific longitudinal volume change computations for establishing brain atrophy rates and lesion evolution over time. Inflammatory disease activity is evaluated by tracking the evolution of FLAIR white matter hyperintensities, T1 white matter hypointensities and, if a gadolinium-enhanced scan is carried out, contrast-enhanced T1 hyperintensities. Furthermore, annualised brain volume changes for whole brain and grey matter, normalised for head size, are provided in comparison to an age- and sex matched normative reference population to evaluate neurodegeneration.

The outputs of the ico**brain ms** software consist of quantitative reports, annotated images, and pre-populated radiological reporting templates (icometrix.com/services/icobrain-ms). These outcomes are provided in the local PACS and available by the time the radiological reading starts.

ico**brain ms** is a registered and certified medical device for clinical use. It is a Class II medical device in the US and Canada, and a Class IIa medical device in Europe under MDR. In the UK, registration to the MHRA was performed by our UK responsible person. ico**brain ms** is a Class I medical device in the UK, based on the medical device risk level to the end user, as set out in Annex IX of the MDD 93/42/EEC (UK MDR 2002).

The use of ico**brain ms** in this study is planned to fall within the scope of the intended use, without additional invasive or burdensome procedures. Therefore, the use of ico**brain ms** is considered non-interventional according to local regulations. We will ensure successful installation of the digital solutions into the clinical workflow at each site prior to patient enrollment within the study. The successful installation of the components includes the following steps:

- ico**brain ms**: installation of ico**bridge** ensuring the transfer of MRI scans from the site's PACS to the ico**metrix** secure cloud
- Radiologists and neurologists will be educated on the use and interpretation of the ico**brain ms** reports

New ico**brain ms** releases may occur from time-to-time and release notes will be available via the ico**brain** website. These changes do not require amendments to the protocol as they are managed with an ISO13485-certified Quality Management System to stay in compliance with applicable regulations (Medical Device Directive [MDD] 2007/47/EC or Medical Device Regulation [MDR] in Europe, 21 CFR part 820 in the US and Medical Devices Regulations SOR/98-282 in Canada). Nevertheless, all updates and upgrades will be filed in the TMF and sent to trial sites for their information and storage in their ISF. Updates to patient-facing material outside of the approved devices will require a protocol amendment and are subject to REC and regulatory authority approval, in accordance with local regulatory requirements.

16.2 Techniques and interventions

See Section 9 for details.

16.3 Tools

Please see Sec 9.4 for descriptions of tests and questionnaires.

17. Safety reporting

Clinical adverse events and serious adverse events will not be reported as these are not relevant for this study.

Apart from adverse events, the study can include incidents due to the medical device quality or other safety related problems with the output of the medical device.

If physicians become aware of incidents due to the medical devices' quality or safety-related problems with the output of the medical devices to protect the users and patients, this should be reported to ico**metrix** via email (support@icometrix.com). These incidents include:

- Any malfunction or deterioration in the characteristics and/or performance of a device, including inadequacy in the labelling
- Any technical or medical reason in relation to the characteristics or performance of a device leading to systematic recall of devices of the same type by the manufacturer
- Privacy incident or personal data breach

ico**metrix** will subsequently inform QMUL based on ico**metrix** SOPs for vigilance and incidence reporting and associated work instructions to inform QMUL. QMUL will be responsible for classifying and reporting the incident to the necessary regulatory authorities (HRA/REC) if required using the appropriate manufacturer incident reports.

17.1 Adverse Events (AEs) and Adverse Device Events (ADEs)

An AE is any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by or related to that intervention. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with study activities. As ico**brain ms** is an assistive device and will not make independent 'decisions' on behalf of patient care (no drugs are tested as part of the study and are all used as approved on-label), AE's will not be reported in this study.

ADE: An adverse device event is an event that caused, or almost caused, an injury to a patient or other person, or a wrong or delayed diagnosis and treatment of a patient. Although direct injury from ico**brain ms** to a trial participant is impossible, it will be noted on a participant's medical file if an ADE affected the MRI reporting. All ADEs are to be documented in the participants' medical notes or other source data documents and the CRF.

17.2 Adverse Reaction (ARs)

An AR is any untoward and unintended response in a participant to an intervention. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the intervention qualify as adverse reactions. The expression 'reasonable causal relationship' means in general that there is evidence or an argument to suggest a causal relationship.

As ico**brain ms** is an assistive device and will not make independent 'decisions' on behalf of patient care (no drugs are tested as part of the study and are all used as approved on-label), AR's will not be reported in this study.

17.3 Notification and reporting of Adverse Events, Reactions and Adverse Device Events

If the ADE is not defined as serious, the ADE will be recorded in the study documents and the participant followed up by the research team. The ADE will be documented in the participants' source documents, the CRF, and, where appropriate, medical records.

As ico**brain ms** is an assistive device and will not make independent 'decisions' on behalf of patient care (no drugs are tested as part of the study and are all used as approved on-label), AE's will not be reported in this study.

17.4 Serious Adverse Events (SAEs), Serious Adverse Device Events (SADEs) and Unexpected Serious Adverse Device Events (USADEs) or reactions

An SAE is defined as an untoward occurrence that:

- Results in death,
- Is life-threatening,
- Requires hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Consists of a congenital anomaly or birth defect, or
- Is otherwise considered medically significant by the investigator.

As ico**brain ms** is an assistive device and will not make independent 'decisions' on behalf of patient care (no drugs are tested as part of the study and are all used as approved on-label), SAE's will not be reported in this study. Similarly, SADEs and USADEs are not applicable for this study as ico**brain ms** cannot cause direct or indirect serious injury.

17.5 Notification and reporting of Serious Adverse Events

Serious Adverse Events (SAEs) that are considered to be 'related' and 'unexpected' will be reported to the sponsor within 24 hours of learning of the event, and to the REC within 15 days in line with the required timeframe.

As ico**brain ms** is an assistive device and will not make independent 'decisions' on behalf of patient care (no DMTs are tested as part of the study and all that are used are approved on-label), SAE's will not be reported in this study.

17.6 Device Deficiencies

All device deficiencies will be recorded on the Clinical investigation device deficiency log and where appropriate in the participant's medical records. This should be reported to ico**metrix** via email (support@icometrix.com).

Device deficiencies which could have caused a SADE must be reported to the sponsor within 24 hours of becoming aware of the event by submitting a Device Reporting Form to research.safety@qmul.ac.uk.

Device deficiencies must be recorded and reported throughout the Clinical Investigation.

17.7 Urgent Safety Measures

The CI will take urgent safety measures if necessary, to ensure the safety and protection of the clinical study participant from immediate hazards to their health and safety. The measures will be taken immediately. The approval of the REC prior to implementing urgent safety measures is not required. However, the CI will inform the sponsor and REC (via telephone) of this event immediately.

The CI will inform the REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office (JRMO)) will be sent a copy of the correspondence with regards to this matter.

17.8 Overview of the Safety Reporting responsibilities

The CI is the medical assessor on behalf of the sponsor and will review all events reported. The CI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

18. Monitoring and auditing

The sponsor or delegate retains the right to audit any study, study site, or central facility. Any part of the study may be audited by the funders, where applicable.

On site monitoring will be performed as per the study monitoring plan. Monitoring will include source data verification.

19. Trial committees

For this trial there will be two overall committees: A Trial Steering Committee (TSC) and a Trial Management Group (TMG) overseeing the trial. The TSC will have a majority independent representation, including the Chair. The TSC committee will meet regularly (in person or virtually) and will send reports to the sponsor. The TMG will be chaired by the CI. The TMG will meet regularly to ensure all practical details of the trial are progressing well, working well and everyone within the trial understands them. Further detail on the membership and full remit of these committees may be found in the TSC and TMG Charters.

These committees will be satisfactory to ensure both patient safety and data oversight bearing in mind the nature of this AI software CE-marked device study.

20. Finance and funding

This study is funded via The Artificial Intelligence in Health and Care Award (AI Award) and is funded via the NIHR **THE SECRETARY OF STATE FOR HEALTH AND SOCIAL CARE** of 39 Victoria Street, Westminster, London, SW1H 0EU.

As part of the study, ico**metrix** will be providing the required software needed to install ico**bridge**. This is the data transfer system that connects to the hospital's PACS. https://icobridge.icometrix.com

21. Indemnity

The insurance that QMUL has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm.

22. Dissemination of research findings

Through external communication, dissemination and exploitation, the results and knowledge of the project will be widespread amongst all the relevant stakeholders across the NHS. Furthermore, the results will be made available to the larger scientific community via peer-reviewed publications in scientific journals and presentations at scientific meetings. Furthermore, the PPI lead will work to develop a clear and accessible communication about project outcomes to the general public and patient groups. Communication and dissemination activities will be designed and implemented in three phases following the project life cycle:

- Raise awareness, focuses on the project objectives and the clinical relevance of MRI biomarkers and their importance in the treatment decision-making
- Project update, provides information about the project status update and preliminary results
- Project results, focuses on the dissemination of the project results.

Results of AssistMS will be presented at national and international meetings, and written up for peer-review. We will also provide summaries in lay language to communicate with pwMS and the wider public via our blog, the MS charities' websites, Twitter/X and other social media. AssistMS will provide evidence of the clinical usefulness of AI-assisted MRI assessment in the care pathway of pwMS. The project will clarify how ico**brain ms** can improve efficiency and quality of radiological assessment, treatment, clinical decision-making and patient outcomes while estimating its potential health economic impact on the NHS. Leveraging the research findings of AI Award supported activities to inform a robust health-economic modelling which will be used to seek appropriate funding support for a better spread of the technology across the NHS including AI Award phase 4 and NICE Diagnostic Assessment Program. The targeted scientific publications are the following: clinical trial protocol, audit, systematic review (the role of AI-driven software tools in clinical practice), the clinical validation of ico**brain ms** and the health economic assessment.

This protocol is based on JRMO Protocol template for Interventional Studies; v4.0 07.04.2022

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