1. PROTOCOL

1.1 Protocol Acronym/Full Title

STRIVE - A multicentre randomi**S**ed controlled **TR**ial of **I**ntra**VE**nous immunoglobulin (IVIg) versus standard therapy for the treatment of transverse myelitis in adults and children

1.2 Trial Identifiers

EudraCT Number:	**2014-002335-34**
ISRCTN Number:	**ISRCTN12127581**
REC Number:	**14/SC/1329**
ClinicalTrials.gov Number:	**NCT02398994**
Funders Number:	**11/129/148**

1.3 Sponsor

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1.6 Committee Members

Committee:	**Trial Steering Committee (TSC)**
Honorary Chair:	Prof Richard Hughes

Members:	Ming Lim (CI) Anu Jacobs (PI)
Independent Members:	Claire Lundy (Paediatric Neurologist) Barbara Babcock (TM Society) Lew Gray (TM Society) Martin Kappler (Statistician) Mark Sanders (Clinician)

Committee:	**Data Management and Ethics Committee (DMEC)**
Honorary Chair:	Prof John Zajicek
Members:	Sarah Cotterill (Statistician) Alasdair Parker (Clinician)

1.7 Study Sites

City	Site Number		Trusts
	Paediatric	Adult	
London - South	01	02	Guy's & St Thomas' NHS Foundation Trust
London - North	03	04	- Great Ormond Street Hospital for Children NHS Foundation Trust - Barts Health NHS Trust
Liverpool	05	06	- Alder Hey Children's NHS Foundation Trust - The Walton Centre NHS Foundation Trust
Oxford	07	08	Oxford University Hospitals NHS Trust
Birmingham	09	10	- Birmingham Children's Hospital NHS Foundation Trust - University Hospitals Birmingham NHS Trust
Cardiff	11	12	Cardiff & Vale University Health Board, NHS Wales
Bristol	13	14	- North Bristol NHS Trust - University Hospital Bristol NHS Foundation Trust
Manchester	15	16	- Central Manchester University Hospitals NHS Foundation Trust - Salford Royal NHS Foundation Trust
Southampton	17	18	University Hospital Southampton NHS Trust
Newcastle	19	20	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Nottingham	21	22	Nottingham University Hospitals NHS Trust
Edinburgh	25	23	Western General Hospital, NHS Lothian
London (cont)		24	King's College Hospital NHS Foundation Trust

2. Study Synopsis

TITLE OF CLINICAL TRIAL:	A multicentre randomi**S**ed controlled **TR**ial of **I**ntra**VE**nous immunoglobulin (IVIg) versus standard therapy for the treatment of transverse myelitis in adults and children
Protocol Short Title/ Acronym:	**STRIVE**
Study Phase If Not Mentioned In Title:	Phase 3
Sponsor Name:	Guy's and St Thomas' NHS Foundation Trust
Chief Investigator:	Dr Ming Lim
Medical Condition Or Disease Under Investigation:	Transverse myelitis (TM) (acute, first onset cases), including first presentation of neuromyelitis optica (NMO)
Purpose Of Clinical Trial:	To conduct a multi-centre, single blind, parallel group randomised-controlled trial to generate evidence to inform clinical and health economic decisions of IVIg use in adults and children with TM.
Primary Objective:	To evaluate if additional and early treatment with intravenous immunoglobulin (IVIg) is of extra benefit in TM when compared to the current standard therapy of intravenous steroids.
Secondary Objective(s):	1. The clinical and para-clinical data collected from patients will provide a robust resource and platform for other clinical studies, including identification of early predictors of poor outcome. 2. Bio banked samples from patients recruited to the study will be collected and used for carefully designed biological studies by a consortium of established basic science researchers in the field.
Trial Design:	A multicentre, single blind, parallel group randomised controlled trial (RCT)
Endpoints:	**Primary endpoint** an improvement of 2 points or greater on the ASIA Impairment scale (classified A-E) at 6 months after randomisation, compared to baseline value measured just prior to randomisation **Secondary endpoints:** Secondary efficacy measures will be assessed at the follow up visit 6 months post randomisation, but are also assessed at 3 and 12 months post randomisation for validation purposes. 1. Change in ASIA motor scale (0-100) and ASIA sensory scale (0-112) 2. Change in Kurtzke's expanded disability status scale (EDSS) measured with Neurostatus scoring 3. EQ-5D-Y for patients aged 8-12 years at presentation 4. EQ-5D-5L for patients aged ≥ 13 at presentation 5. Individuals ≥ 13 years: International SCI Quality of Life Basic Data Set 6. Client Service Receipt Inventory (CSRI)

	Tertiary endpoints: Tertiary efficacy measures will be assessed at the follow up 6 months post randomisation, but are also assessed at 12 months for validation purposes: 1. International SCI Bladder/Bowel Data Set for patients aged ≥13, 2. Paediatric Quality of Life Inventory™ (PedsQL Parent Report for Toddlers) for children 2-4 years at presentation 3. Paediatric Quality of Life Inventory™(PedsQL Parent Report for Young Children) for children aged 5-7 years at presentation 4. Individuals ≥ 13 years of age at presentation: International SCI Pain Basic Data Set
Sample Size:	170
Summary Of Eligibility Criteria:	Patients will be eligible for inclusion in the trial if on presentation they: • Are aged 1 year or over • Have been diagnosed with: *EITHER* acute first onset transverse myelitis (The TM CONSORTIUM WORKING GROUP 2002 criteria for probable TM will be used. Hence, following clinical and radiological exclusion of a compressive myelopathy, patient will be diagnosed to have TM if they meet all the following criteria: ▪ Sensory, motor, or autonomic dysfunction attributable to spinal cord disease ▪ Bilateral signs and/or symptoms (not necessarily symmetric) ▪ Sensory level (except in young children <5 years where this is difficult to evaluate) ▪ L ack of MRI brain criteria consistent with MS (McDonald 2010 space criteria) ▪ Progression to nadir between 4 h and 21 days) *OR* Have been diagnosed with first presentation of neuromyelitis optica. (Patients with definite modified NMO will meet the following criteria (Wingerchuk et al, 2006). Absolute criteria, both: 1. Optic neuritis 2. Acute myelitis Plus two out of three supportive criteria: i. Brain MRI not meeting criteria for MS at disease onset ii. Spinal cord MRI with contiguous T2-weighted signal abnormality extending over three or more vertebral segments, indicating a relatively large lesion in the spinal cord iii. Aquaporin 4 seropositive status) • Have an ASIA Impairment score of A, B or C • Have commenced steroid treatment but will be randomised no later than day 5 of steroids, and if definitely known, randomisation will not exceed 21 days from the onset of symptoms • Give assent(<16 years)/consent to participate in the

	trial
Summary Of Exclusion Criteria:	Patients would be excluded if they show evidence of: • Contraindication to IVIg as stated in the product SmPC, or receiving IVIg for other reasons • Previously known systemic autoimmune disease (eg systemic lupus erythematosus) or any evidence of systemic inflammation during current presentation. • Direct infectious aetiology (eg varicella zoster) • Previous episode of CNS inflammatory demyelination • Acute disseminated encephalomyelitis (ADEM) • Other causes of myelopathy not thought to be due to myelitis (eg nutritional, ischaemic, tumour etc.) • Other disease which would interfere with assessment of outcome measures • Known pregnancy • Circumstances which would prevent follow-up for 12 months
IMP, Dosage And Route Of Administration:	Patients randomised to the **control arm** of this study will be prescribed intravenous methylprednisolone as per standard medical care. Paediatric patients would receive 30 mg/kg or 500 mg/m^2 capped to a maximum dose of 1 g/day for 5 days. Adult patients will be given 1 gram/day for 5 days. Variations in practice will be recorded. Patients in the **intervention arm** will receive the above standard therapy and in addition, IVIg: 2 g/kg will be administered in 5 divided doses (or given over 2 doses in children. ≤ 41.2kg).
Maximum Duration Of Treatment Of A Subject:	Interventional treatment (IVIg) 2-5 days, follow-up 12 months
Version And Date Of Final Protocol:	v5.0 27/11/2015
Version And Date Of Protocol Amendments:	V2.0 30/09/2014 V2.1 15/10/2014 V3.0 15/01/2015 v4.0 30/06/2015

3. Glossary of terms

ADEM	Acute disseminated encephalomyelitis
AE	Adverse Event
AQP 4	Aquaporin 4
AR	Adverse Reaction
ASIA	American Spinal Injury Association
CI	Chief Investigator
CNS	Central nervous system
CRF	Case report form
CSF	Cerebrospinal fluid
CSRI	Client Services Receipt Inventory
CTU	Clinical Trials Unit
ED 5Q	Euro Quality of Life Health Questionnaire
EDSS	Expanded Disability Status Scale
EMEA	European Medicines Agency
ICC	Intra-cluster correlation coefficient
IME	Important Medical Event
IVIg	Intravenous immunoglobulin
IV-MP	Intravenous methylprednisolone
LMM	Linear mixed modelling
MAR	Missing at randomisation
MHRA	Medicines and Healthcare Products Regulatory Agency
NMO	Neuromyelitis optica
PedsQL	Paediatric Quality of Life Questionnaire
PI	Primary Investigator
PIS	Patient Information Sheets
PLEX	Plasma exchange
RCT	Randomised controlled trial
SAE	Serious Adverse Event
SCI QoL	Spinal Cord Injury Quality of Life Questionnaire
SmPC	Summary of product characteristics
SUR	Serious Unexpected Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TM	Transverse myelitis
UAR	Unexpected Adverse Reaction

4. Contents

5. Background

5.1 Background

Transverse myelitis (TM) is an immune-mediated disorder of the spinal cord affecting children and adults, characterised by a rapid onset of paraplegia or tetraplegia, loss of sensation and sphincter disturbance. Attacks usually develop over 24 hours, and in some cases can progress rapidly to a potentially devastating and sometimes life threatening condition. The severity of symptoms depends on the spinal cord level affected, where patients with high cervical lesions often require intensive care support to maintain respiratory function. Patients can recover fully from TM but a large number are left with significant disability. Recovery occurs within weeks of onset of symptoms and is most rapid during the first 3–6 months, although further improvement may be seen up to 2-4 years (reviewed in Borchers and Gershwin, 2012). Neuromyelitis-optica (NMO) is an uncommon relapsing condition where transverse myelitis can be the first presenting symptom. Neurodisability accrues with progressive relapses. NMO is the first inflammatory demyelinating condition to have a specific and sensitive biomarker (aquaporin-4 antibodies) measured in serum.

The precise numbers that make full recoveries from TM remains unclear. Studies prior to the TM Consortium Working Group criteria, may have included patients with a wider range of myelopathies such as spinal cord infarction (Altrocchi 1963), or may reflect the greater severity of cases seen at a tertiary referral centre such as the John's Hopkins TM Centre (Kaplin et al, 2005), where up to 20% are reported to make a good recovery. Currently, the only report to reliably inform on the outcome of adult onset TM is a retrospective French multicentre study applying TM Consortium Working Group criteria, where 36% of patients with TM had a poor prognosis as defined by death or non-ambulating (de Seze et al, 2005). In children, approximately half make a good recovery (reviewed in Absoud et al, 2013a). Hence, the majority of adults and children presenting with TM either have a fair outcome, (functional and ambulatory, but with varying degrees of spasticity, urgency and/or constipation, and some sensory signs) or worse (remaining completely or largely unable to walk, having at best partial sphincter control, and being left with severe sensory deficits [as reviewed in Borchers and Gershwin, 2012]). These results represent a huge burden on patients and, of course, their carers. With conservative estimates of incidence of TM in UK being 350/year (based on incidence of 3-7/million; Young et al, 2009 and Absoud et al, 2013b), this clearly imposes a significant cumulative demand on the health resources in the UK. Moreover, many patients are affected at peak ages that reflect their prime working life, thus resulting in loss of productivity and imposing a further financial impact on the country.

Importantly, strategies to reduce the disability in patients are urgently required, yet there are no robust controlled trials, in children or adults, to inform on its optimal treatment. The current clinical consensus is derived from data that are mainly extrapolated from class IV evidence from case series or clinical trials for the treatment of exacerbations of adult multiple sclerosis (TM Consortium Working Group, 2002, Greenberg et al, 2007, Frohman and Wingerchuk, 2010, Scott et al, 2011). In adults, this suggests that treatment of relapses with intravenous methylprednisolone shortens relapse duration and speeds recovery. It is from this that the current standard therapy has been based whereby, in both children and adults, treatment with high

dose intravenous steroids is prescribed for 3-7 days to reduce inflammation, hasten recovery and restore neurological function.

Although IV steroids are now the most common treatment for TM, there are other available interventions which have proved effective in aiding recovery, but which are not routinely applied. In a retrospective analysis of 122 adults with TM, acute therapies given at one centre between 2001 and 2005 were evaluated, with the finding that some patients benefited from the addition of plasma exchange (PLEX) to intravenous methylprednisolone (Greenberg et al, 2007). The efficacy of PLEX was also demonstrated in a small randomised controlled trial in adults with acute central nervous system (CNS) demyelination (including 4 patients with TM) where steroids had failed to induce a remission of symptoms (Weinshenker et al, 1999). However, administering PLEX is technically difficult and costly, making it challenging to deliver within the NHS, resulting in it not being universally available.

Treatment with intravenous Immunoglobulin (IVIg) is also used increasingly in the management of a range of neurological conditions, and its efficacy has been established clearly in randomised controlled trials for a handful of these conditions (Hughes et al, 2009). In adults and children with CNS demyelination who do not respond to steroids, IVIg is often used, although supporting data is limited to small case series and single case reports (Banwell et al, 2007, Elsone et al, 2014). The most relevant actions of IVIg in the therapy of neurological diseases include: (a) inhibition of complement binding, (b) neutralization of pathogenic cytokines, (c) down-regulation of antibody production, and (d) modulation of Fc-receptor mediated phagocytosis. Additional actions include modulation of T-cell function and enhancement of remyelination (Dalakas 1998). The majority of these factors are common across inflammatory disorders of the CNS including transverse myelopathy (Awad and Stuve 2011), providing a strong rationale for its use in the management of TM. In addition, IVIg is cost effective when compared to PLEX and more readily accessible.

Here, we aim to conduct a multi-centre, single blind, parallel group randomised-controlled trial to generate evidence to inform clinical and health economic decisions of IVIg use in adults and children with TM.

5.2 Risks and Benefits

Risks: This study will include adults and children. As treatments in both arms of the trial are already used in current clinical practice, those participating will face almost no additional risk beyond what they would experience in treatment outside the trial.

Benefits: Interventions that can reduce the disability in patients are urgently required. The current management recommendation is largely based on expert opinion (Scott et al, 2011), as there remain no robust controlled trials for the treatment of TM, in children or adults, to inform on the optimal treatment of TM. This trial seeks to evaluate if IVIg would be beneficial in the management of TM.

6. Trial Objectives and Design

6.1 Trial Objectives

The **primary objective** of this single blind, parallel group randomised controlled trial is to evaluate if additional, and early, treatment with IVIg is of extra benefit in TM when compared to the current standard therapy of intravenous steroids.

In addition, our **secondary objectives** are to provide benefits whereby:

1. The clinical and para-clinical data collected from patients will provide a robust resource and platform for other clinical studies, including identification of early predictors of poor outcome.
2. Bio banked samples from patients recruited to the study will be collected and used for carefully designed biological studies by a consortium of established basic science researchers in the field.

6.2 Primary endpoint measure

An improvement of 2 points or greater on the ASIA Impairment scale (classified A-E) at 6 months after randomisation, compared to the value measured at baseline just prior to randomisation.

6.3 Secondary endpoint measures

1. Change in ASIA motor scale (0-100) and ASIA sensory scale (0-112) at 3, 6, and 12 months post randomisation
2. Change in Kurtzke expanded disability status scale (EDSS) measured by Neurostatus scoring at 3, 6, and 12 months
3. EQ-5D-Y for patients aged 8-12 years (at presentation) at 3,6 and 12 months
4. EQ-5D-5L for patients aged ≥ 13 years (at presentation) at 3, 6 and 12 months
5. Individuals ≥ 13 years at presentation: International SCI Quality of Life Basic Data Set at 3, 6 and 12 months
6. Client Service Receipt Inventory (CSRI) at 3, 6 and 12 months

6.4 Tertiary endpoint measures

1. International SCI Bladder/Bowel Data Set for patients aged ≥13 years at presentation to be completed at 6 and 12 months post randomisation
2. Children 2-4 years of age at presentation: Paediatric Quality of Life Inventory™ (PedsQL Parent Report for Toddlers) at 6 and 12 months
3. Children 5-7 years of age at presentation: Paediatric Quality of Life Inventory™ (PedsQL Parent Report for Young Children) at 6 and 12 months
4. Individuals ≥ 13 years of age at presentation: International SCI Pain Basic Data Set at 6 and 12 months

6.5 Trial Design

This is a UK multi-centre, single blind, parallel group randomised controlled trial.

Patients randomised to the **control arm** of this study will be prescribed intravenous methylprednisolone in line with local clinical practice. Recommended dosages are listed below; any variations from this practice will be recorded.

- Paediatric patients will receive 30 mg/kg or 500 mg/m^2 capped to a maximum dose of 1 g/day for 5 days.
- Adult patients will be given 1 gram/day for 5 days.

Patients in the **intervention arm** will receive the above standard therapy *plus* additional IVIg:

- In adults, 2 g/kg will be administered in 5 divided doses
- In children who are > 41.2kg, 2g/kg will be administered as above in adults; in children who are ≤ 41.2kg, 2g/kg will be administered in 2 divided doses

IVIg dosing does not need to be administered over consecutive days but must be administered according to the dosing schedule (Appendix 1).

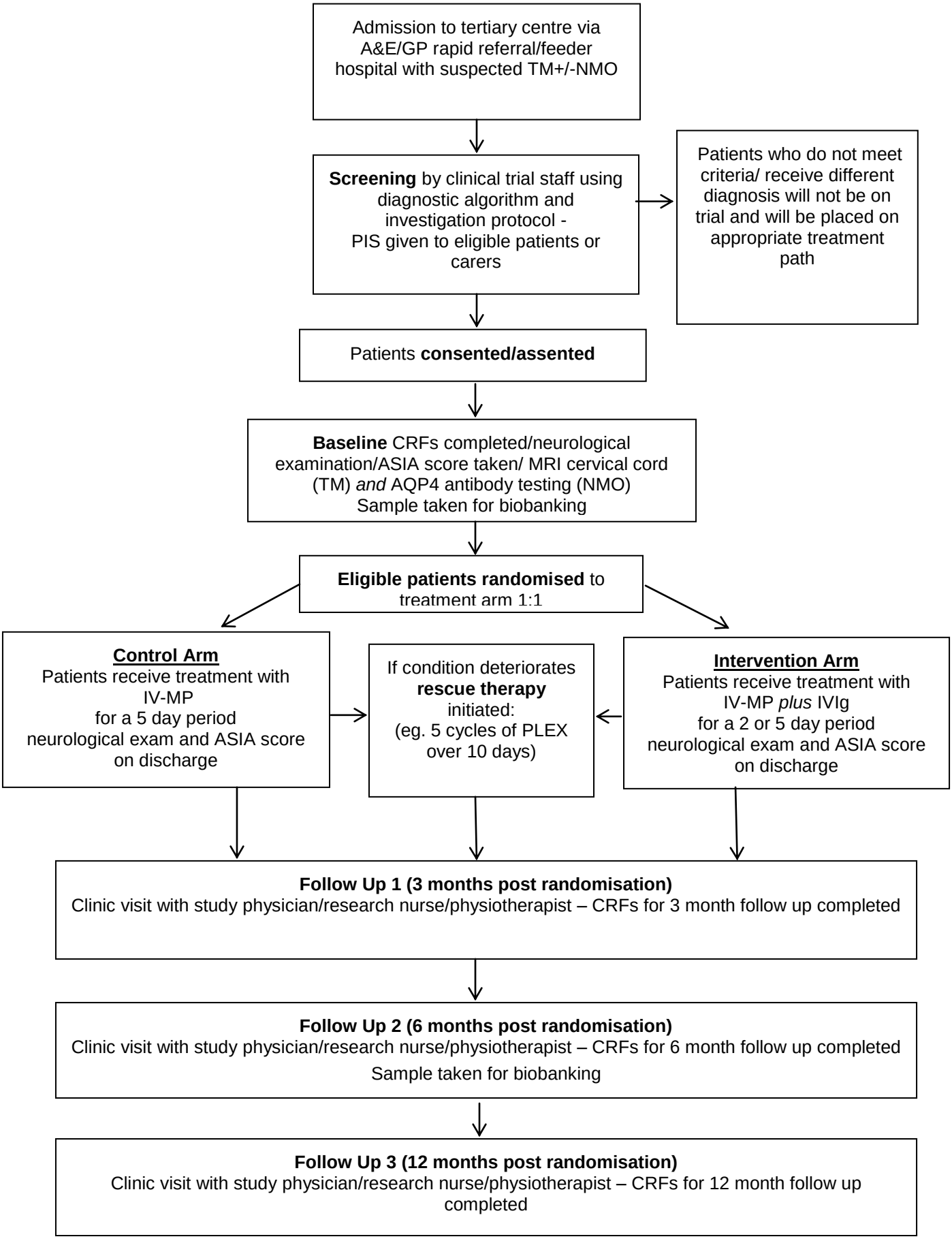
Patients may be recruited and randomised up to 5 days from the date of first commencing steroid therapy or up to 21 days from the onset of symptoms (if definitely known).

In patients who do not respond to standard IV MP treatment or adjunctive treatment with IVIg, rescue therapy, such as PLEX, will be instituted.

If PLEX is administered, such a therapy will attenuate treatment effect of IVIg, and may indeed have a treatment effect of its own, guidance parameters will be set out to define and standardise PLEX regime. Briefly:

- Treatment failure should be considered if no improvement is seen or deterioration occurs, after 14 days from presentation or 5 days after completion of either treatment arm.
- A complete PLEX treatment should comprise of at least 5 cycles, of which in each cycle at least 75% of plasma volume is exchanged, with a 24-48 hour interval between each cycle.
- An extra course of intravenous methylprednisolone may be given by physicians, often during the lag phase, from decision to proceed with rescue therapy to its initiation (usually 5-7days).

6.6 Participant Flowchart



6.7 Definition of End of Study

The end of the study is defined as the last participant's final assessment at T4, 12 months after randomisation.

7. Trial Medication

7.1 Investigational Medicinal Product

Investigational medicinal product will be provided as human normal immunoglobulin (Intratect®) 100g/l solution for infusion in single 5g (50ml) or 10g (100ml) glass vial. Biotest Pharma GmbH, marketing authorisation holder of Intratect®, will be providing the commercially available Intratect® for use in the trial.

Annex 13 clinical trial labelling exemption is in place and approved by the Medicines and Healthcare Products Regulatory Agency (MHRA). A standard pharmacy dispensing label will be applied to the IMP at the point of dispensing by pharmacy at each investigator site.

The site pharmacies are responsible for the safe and appropriate storage of IMP at the site in accordance with manufacturers' instructions. IMP should be stored in a secure area with limited access. Storage conditions should be monitored on a regular basis according to local arrangements.

Intratect® should be stored in accordance to manufacturers' instructions:

- Do not store above 25 °C.
- Do not freeze.
- Keep the vial in the outer carton, in order to protect from light.

Refer to the summary of product characteristics of Intratect® at https://www.medicines.org.uk for further information.

Participating sites will be sent initial stocks of Intratect® and all subsequent ordering will be manually requested via the trial manager. Pharmacists will be responsible for notifying the trial manager when IMP stock is getting low. Biotest will distribute the IMP directly to pharmacies at individual participating sites upon written request via a shipment request form from the trial manager. Participating site' pharmacists will notify the trial manager of the receipt of the IMP in an email containing relevant data (IMP batch number, date of receipt, expiry date).

Please note that intravenous methylprednisolone (as sodium succinate) is classed as non-investigational medicinal product in this trial. The product should be dispensed by hospital pharmacies in accordance to standard clinical practice.

7.2 Dosing Regimen

Intravenous methylprednisolone (as sodium succinate) will be administered in accordance with local clinical guidelines. A single daily dose of 30mg/kg or 500mg/m^2 (maximum 1 g/day) for 5 days can be used in paediatric patients. Adult patients can receive 1g/day for 5 days. Variations of this recommendation will be recorded.

Patients randomised to the control arm will receive no additional treatment.

Patients randomised to the treatment arm will receive the above treatment with IV-MP *plus* IVIg 2g/kg in divided doses as listed in **Appendix 1.**

7.3 IMP Risks

IMP risks can be found in the Intratect® SmPC at https://www.medicines.org.uk (current data included in **Appendix 4**).

7.4 Drug Accountability

Responsible site personnel must maintain accurate accountability records of the IMP, including, but not limited to, the number of vials received, the number of vials dispensed to which subject, batch number, expiry date, and date of transaction.

As subject compliance can be fully established, all used IMP will be disposed of locally immediately following administration in accordance to local requirements. Disposal of unused IMP is only permitted with sponsor's authorisation.

7.5 Subject Compliance

Treatment with the IMP will be administered under the supervision of the investigator and in a controlled clinical environment; therefore, full patient compliance with treatment is anticipated in this trial.

7.6 Concomitant Medication

Only relevant immuno-modulatory medications are to be recorded throughout the study, and these should be captured on the Concomitant Medications form.

In patients who do not respond to control treatment or adjunctive treatment with IVIg, rescue therapy will be instituted, in accordance with local guidelines (please see section 6.5 above). In most cases the rescue therapy of choice will be PLEX therapy. This will also be recorded as a concomitant medication.

Noteworthy interactions with IVIg include:

1) Live attenuated virus vaccines: Immunoglobulin administration may impair the efficacy of live attenuated virus vaccines such as measles, rubella, mumps and varicella for a period of at least 6 weeks and up to 3 months. After administration of this product, an interval of 3 months should elapse before vaccination with live attenuated virus vaccines. In the case of measles, this impairment may persist for up to 1 year. Therefore, patients receiving measles vaccine should have their antibody status checked.

2) Interference with serological testing: After injection of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may result in misleading positive results in serological

testing. Passive transmission of antibodies to erythrocyte antigens, e.g. A, B D may interfere with some serological tests including the antiglobulin test (Coomb's test).

Details of all other agents that might interact with Intratect® are listed in the SmPC at https://www.medicines.org.uk.

8. Selection and Withdrawal of Subjects

8.1 Inclusion Criteria

Patients will be eligible for inclusion in the trial if on presentation they:

- Are aged 1 year or over
- Have been diagnosed with:
  EITHER acute first onset transverse myelitis
  (The TM CONSORTIUM WORKING GROUP 2002 criteria for probable TM will be used. Hence, following clinical and radiological exclusion of a compressive myelopathy, patient will be diagnosed to have TM if they meet all the following criteria:
    - Sensory, motor, or autonomic dysfunction attributable to spinal cord disease
    - Bilateral signs and/or symptoms (not necessarily symmetric)
    - Sensory level (except in young children <5 years where this is difficult to evaluate)
    - Lack of MRI brain criteria consistent with multiple sclerosis (McDonald 2010 space criteria)
    - Progression to nadir between 4 h and 21 days

  OR Have been diagnosed with first presentation of neuromyelitis optica.
  (Patients with definite modified NMO will meet the following criteria (Wingerchuk et al, 2006).
  Absolute criteria, both:
    1. Optic neuritis
    2. Acute myelitis

  Plus two out of three supportive criteria:
    i. Brain MRI not meeting criteria for MS at disease onset
    ii. Spinal cord MRI with contiguous T2-weighted signal abnormality extending over three or more vertebral segments, indicating a relatively large lesion in the spinal cord
    iii. Aquaporin 4 seropositive status)
- Have an ASIA Impairment Score of A-C
- Have commenced steroid treatment but will be randomised no later than day 5 of commencing treatment, and if definitely known, randomisation will not exceed 21 days from the onset of symptoms
- Give assent (<16 years)/consent to participate in the trial

8.2 Exclusion Criteria

Patients would be excluded if they show evidence of:

- Contraindication to IVIg as stated in the product SmPC, or receiving IVIg for other reasons
- Previously known systemic autoimmune disease (eg systemic lupus erythematosus) or any evidence of systemic inflammation during current presentation.
- Direct infectious aetiology (eg varicella zoster)
- Previous episode of CNS inflammatory demyelination
- Acute disseminated encephalomyelitis (ADEM)
- Other causes of myelopathy not thought to be due to myelitis (eg nutritional, ischaemic, tumour etc.)
- Other disease which would interfere with assessment of outcome measures
- Known pregnancy
- Circumstances which would prevent follow-up for 12 months

Spinal cord inflammation demonstrated by CSF pleocytosis or elevated IgG index or gadolinium-enhanced MRI is supportive of an inflammatory aetiology but will not be essential for inclusion/exclusion. Aquaporin-4 antibodies will be tested in all individuals with myelitis, as NMO can present as isolated transverse myelitis. In addition, patients will also have investigations that are clinically indicated to identify specific non-inflammatory aetiologies.

8.3 Selection of Participants

Participants will be individuals who meet the inclusion criteria/diagnostic algorithm (**Appendix 2**), presenting to the catchment area of participating tertiary neurology centres, though some neurologists may also recruit patients at district general hospitals or from rapid GP referrals. There are 12 tertiary paediatric neurology and 13 tertiary adult neurology services spanning 12 regions, chosen for geographic distribution, established research infrastructure and for having investigators with an active record of accomplishment in recruiting to network supported studies (section 1.7). These centres cover approximately half of the UK population. Hence if the UK incidence of TM patients is approximately 350 per year, a recruitment period of 2.5 years, with a recruitment rate of 35% of eligible patients is expected to achieve the required sample size of n=170.

8.4 Withdrawal of Subjects

The patient, or their parent/guardian, has the right to withdraw from the study at any time for any reason. In the event that a participant withdraws from the study (i.e. refuses further treatment/outcome data collection) a withdrawal form must be completed.

The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAEs, and SUSARs, subsequent evidence of a different aetiology, protocol violations, cure, administrative or other reasons. Participants who wish to/must discontinue *study medication* will be returned to standard care via their supervising physician, but will continue to provide study specific data at follow up visits at 3, 6 and 12 months.

It is understood that an excessive rate of withdrawals can jeopardise randomisation outcomes and render the study results uninterpretable; therefore, unnecessary withdrawal of patients will be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

8.5 Expected Duration of Trial

It is anticipated that the project will take 3.5 years and will be managed through the King's Clinical Trials Unit. Patient recruitment will take place over the first 30 months, and as each patient will be followed up for one year, collection of data will continue until 42 months following the start date. In the following 12 months (42-54 months from start date), the study team will develop health economic model structure, run model, sensitivity analysis, and complete write up of economic analysis. Importantly, timely trial analysis will be followed by results dissemination.

9. Trial Procedures

9.1 Study Flow Chart

Schedule of Procedures and Data Collection time points

For every time point in the study there are a number of questionnaires/ exam forms that need to be completed as shown in the ***Schedule Table*** below. Some of the questionnaires are intended for particular age groups and when referring to age always use *age at presentation.* Please refer to **Appendix 3** for detailed study procedures.

Schedule Timepoint (T)	**T0** (Screening, baseline and prediagnosis tests)	**T1** (Treatment and discharge)		**T2** 3M	**T3** 6M	**T4** 12M	Ongoing
		*Rescue therapy	Discharge				
Screening with diagnostic algorithm & core investigations including physical exam	**x**						
Patient information and informed consent	**x**						
Eligibility form	**x**						
Registration form	**x**						

Pre-diagnosis Tests – eg. MRI & AQP4	x						
Randomisation	x						
Biobank samples	x				x		
ASIA Impairment Score (A-E)	x	x	x	x	P	x	
ASIA Motor and Sensory Score	x	x	x	x	S	x	
Neurostatus scoring (Kurtzke functional systems and EDSS)	x		x	x	S	x	
8-12 yrs EQ-5D-Y Questionnaire†	x			x	S	x	
≥13 yrs EQ-5D-5L Questionnaire†	x			x	S	x	
CSRI Questionnaire†				x	S	x	
≥13 yrs SCI QoL Basic dataset†				x	S	x	
≥13 yrs SCI Bladder Basic dataset					T	x	
≥13 yrs SCI Bowel Basic dataset					T	x	
≥13 yrs SCI Pain Basic dataset†					T	x	
5-7 yrs Peds QL Questionnaire†					T	x	
2-4 yrs Peds QL Questionnaire†					T	x	
Treatment form			x				
Concomitant medications							x
Discharge form			x				
*Rescue therapy form (if needed)		x					
*Relapse form (at any time point if needed)			x	x	x	x	
Adverse events							x
Study Status Form				x	x	x	
*Withdrawal form (at any time point)							x

Key: P – primary measure, S – secondary measure, T – tertiary measure

*** Rescue therapy, relapse and withdrawal forms may only be necessary for a small subset of patients.**

† Please provide a Stamped Addressed Envelope to participants who cannot complete the questionnaires in clinic. The questionnaires should be then completed at home and posted back to the local research team within one week of the visit.

Appendix 3 lists all examinations and forms needed at screening, consent, randomisation, treatment and follow-up visits.

9.2 Blinding

Due to the technical challenges of masking IVIg from saline, the need for rapid recruitment and the fact that follow-up will be many months after the event using objective well-defined clinical endpoints; treatment will not be blinded (no placebo). The trial manager, pharmacy, and those administering treatment are not blinded; whilst staff carrying out primary outcome assessments at follow-up and statistical analyses will be blinded to intervention.

Screening, baseline and discharge assessments will be made in the tertiary centres by a study physician/research nurse. Following discharge from treatment in hospital, all primary outcome assessments at follow up in clinic at the tertiary centre or appropriate neurology centre, will be carried out by a study physician/research nurse/physiotherapist who has been blinded to treatment. For consistency, wherever possible, the same blinded assessor should carry out the assessments at each time point.

Although not mandatory secondary and tertiary outcome assessments should be performed by a blinded member of staff at follow-up wherever possible.

9.3 Laboratory Tests

All consenting patients will have samples taken for clinical investigations and samples for biobanking, at baseline and at the 6 month follow up. In those cases where samples for clinical investigations have been taken prior to consent, any left-over material will be used for biobanking. No additional samples will be collected unless there is a clinical indication to do so. Samples for biobanking will consist of CSF via lumbar puncture, and blood taken by venepuncture for serum, plasma, DNA, Peripheral Blood Mononuclear cells (PBMC) and RNA (site dependent), and will be stored in one of the two biobanks (London or Cardiff). These samples will not form part of this trial, but are for further hypothesis driven biological research, directed by Neil Robertson and Gavin Giovannoni (adults) and Ming Lim (paediatrics). For the bio-banking procedures, a biobanking guideline will be provided to all investigators.

9.4 MRI Sequences

As part of the routine diagnostic process for TM/NMO, brain and spinal cord sequences should be acquired, the results of which will be used in the study's diagnostic algorithm at screening and if the patient enters the trial, will be recorded as study data. Local protocols will be in place for the acquisition of MRI sequences, which would usually include gadolinium enhanced sequences in the event of a suspected TM/NMO.
To facilitate systematic accrual of neuroimaging information it is recommended that reports include:

1. Location of the lesion (which spinal cord level)
2. Size of the lesion (in terms of how many vertebral segments)
3. Whether gadolinium injection was used and if so, was enhancement seen

During the trial period, the study team may request anonymized patients scans to be provided on a CD to resolve potential clinical and radiological uncertainties.

10. Assessment of Efficacy

10.1 Efficacy Parameters

Primary, secondary and tertiary parameters will be assessed at appropriate time points as listed in Study synopsis and Trial Objectives (sections 2 and 6 respectively) of this protocol.

10.2 Procedures for Assessing Efficacy Parameters

Primary outcome assessments will be carried out by a physician/research nurse/physiotherapist blinded to treatment, secondary and tertiary outcome assessments will be carried out by a blinded member of staff wherever possible, but can be performed by an unblinded person if necessary. All assessments will be reported using the appropriate assessment tools and questionnaires.

10.3 Scales and Training

The standardized American Spinal Injury Association (ASIA) impairment scale, is the currently internationally accepted scale for the measurement of disability in TM (Maynard et al., 1997, Graves et al., 2006). The recently published common data elements recommendations for spinal cord injury recommend the ASIA scale as the primary outcome measure for disability (www.commondataelements.ninds.nih.gov/SCI.aspx). The grading (A-E) is based on determining: sensory levels; motor levels; neurological level of injury; and whether the injury is complete or incomplete. The motor and sensory scales (scored 0-100/0-112) rely on more detailed sensory and motor examinations. In this trial the ASIA Impairment Score (AIS) is the main eligibility criterion as well as the primary outcome.

Each assessor needs to have training and obtain certification for ASIA Sensory and Motor Scoring evaluation (see: http://lms3.learnshare.com/home.aspx). The ASIA website (www.asia-spinalinjury.org) provides learning tools as well as a module which must be completed by examiners involved in the trial and will be provided free of charge.

A working guideline for ASIA assessment has been produced for the trial and will be provided to all investigators.

Neurostatus scoring (Kurtzke's Functional Systems and Expanded Disability Status Scale) is one of the secondary endpoints in the study. The training manuals and CDs together with exam sheets will be made available to each study site ahead of time.

All training must be recorded in the Staff Training Log in the Individual Site Files.

11. Assessment of Safety

11.1 Procedures for Recording and Reporting Adverse Events

11.1.1 Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE):

Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR):

Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR):

An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) for Intratect™ at www.medicines.org.uk.

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (SUSAR):

- Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:
- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

Hospitalisation as a result of the progression of TM and any proceeding medical condition are not considered to be SAEs and should be reported as an AE in the normal way (see below), on the Adverse Event form.

Important Medical Events (IME): Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

11.1.2 Reporting Responsibilities

Organisations have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP-CTO).

SAEs, SARs and SUSARs

Reporting all SAEs, SARs, SUSARs and IMPs

Study staff must report all SAEs, SARs and SUSARs IMMEDIATELY, and certainly no later than 24hrs of the investigator learning of the event (excepting those specified in protocol as not requiring reporting) on the SAE form, then scan and email or fax them to the KHP-CTO at jcto.pharmacovigilance@kcl.ac.uk or Fax 0207 188 8330.
An acknowledgment of receipt will be emailed/faxed back by the KHP-CTO.

The SAE form can be found on the KHP-CTO website www.khpcto.co.uk under the 'SAE Reporting' tab and by opening the pdf called 'Serious Adverse Event Reporting Form'.

On-Reporting: The KHP-CTO will on-report all SAEs, SARs and SUSARs to the Chief Investigator by email, and the Chief Investigator will advise or sign off the event/reaction. The KHP-CTO will report all SUSARs to the MHRA.

Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.
- The CI will notify the chair of the DMEC of all SUSARs and any SAEs that he considers to be of significant safety concern and will report to the relevant ethics committee.

AEs, ARs and UARs

Study staff should record all AEs, ARs and UARs on the Adverse Event log, and via eCRF.

Staff should aim to upload AEs/ARs/UARs and SAEs/SARs/SUSARs (once reported to the KHP-CTO), to eCRFs on the CTU database within 7 days.

The period for reporting all AE and SAE etc. will be from the first administration of the IMP until the patient completes the trial at T3, 12 months after randomisation, or withdrawal of participation.

The Chief Investigator and KHP-CTO (on behalf of the sponsors), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

11.2 Adverse events that do not require reporting

As all medicines in this trial are licensed, most adverse drug reactions that occur, whether serious or not, will be expected treatment-related side effects. IVIg has a well-established side effect profile in the product SmPC at www.medicines.org.uk. A list of the most common side effects can be found in **Appendix 4**.

11.3 Treatment Stopping Rules

The trial may be prematurely discontinued by the Regulatory Authority based on new safety information or for other reasons given by the Data Monitoring & Ethics Committee / Trial Steering Committee regulatory authority or ethics committee concerned. The trial may also be prematurely discontinued due to lack of recruitment or upon advice from a Trial Steering Committee (if applicable), who will advise on whether to continue or discontinue the study and make a recommendation to the sponsor.

12. Statistical considerations

A comprehensive statistical analysis plan will be developed and agreed with the trial's oversight committees. Descriptive analysis (e.g. summary statistics and plots) will be performed to investigate the distribution of the primary outcome, ASIA Impairment Scale score, across participants.

12.1 Sample size considerations and calculation

In recognition of TM as a rare condition, the power analysis has taken into account the inclusion of a futility analysis to be undertaken after recruitment of one third of the target sample. We have assumed that the proportion of participants showing a 2 point improvement (or greater) on the ASIA Impairment scale will be approximately 0.5 (50%) in the control arm and a minimum of 0.75 (75%) in the intervention arm. The sample size calculation is based on the conservative assumption of no correlation between repeated measures.

Randomised 1:1, the primary ITT analyses will compare 76 treatment and 76 control patients, on the ASIA classification scale at 6 months post randomisation. Based on comparing the difference in the number of successes among treatment and controls the SAS *sample size – chi* procedure examines all 77^2 possible trial outcomes under the null and alternative hypotheses. The possible outcomes are then arranged in descending order and cumulative probabilities for every possible value from 76 to -76 are computed. Using a critical value that maintains the tail probability at .02355 under the null the probability under the alternative is 0.9034. The study thus has 90% power for a two-tailed test with alpha=0.05.

The sample size will be inflated for attrition, based on our experience and the design in place to minimise any loss to follow up we estimate 10% attrition. **This would require recruiting a sample size of (n=152/0.90) = 170 (85 participants per arm).**

The ASIA total motor score (0-100) is a secondary outcome. There is little evidence in acute transverse myelitis to summarise this in terms of variance, mean and correlation. Stata *sampsi* indicates that using ANCOVA, with a baseline to endpoint correlation of 0.6, there will be 87% power to detect a difference between the control and treatment arms of a medium to large effect size of 0.4. Such a difference will be of clinical significance.

12.2 Randomisation

Treatment allocation will be stratified at randomisation, by service type (adult or child) using stratified block randomisation; the block will randomly vary in size. Treatment allocation will be at a ratio of 1:1.

12.3 Statistical Analysis

12.3.1 Statistical analysis overview

All analyses will be pragmatic and follow the intention to treat (ITT) principle, that is, patients will be analysed in the groups to which they were randomised irrespective of treatment amount or treatment quality received, utilising all available follow-up data from all randomised patients. Sensitivity analyses will be used to assess the robustness of conclusions to missing outcome data and to departures from randomised treatment.

An interim futility analysis will be conducted after 52 patients have provided a response (26 on each treatment arm), the endpoint being a two point change in the ASIA scale 6 months after randomisation; the results will be assessed by the Data Monitoring Committee. A trial statistician who will be unblinded, will run the prepared syntax to generate the estimates at this interim stage for evaluation by the DMEC. The primary trial statistician will remain blinded and therefore will not take part in this analysis.

If the study continues to full recruitment, the final analyses of effectiveness will be conducted once the trial database has closed. The Data Monitoring Committee will collate effectiveness and safety data during the trial to inform their recommendations to the Trial Steering Committee. All analyses will be completed in Stata and SAS and utilise 2 sided 5% significance tests. Main effects will be summarised by intervention arm and assessment time point with associated 95% Confidence Intervals.

12.3.2 Primary and secondary analysis

The main objective of the statistical analyses is to assess the effect of IVIg on the primary outcome, a 2 point change from baseline on the ASIA classification (A-E) scale, at 6 months post randomisation. To this end mixed effects logistic regression will be employed. In such models, the binary outcome variable measured at the post treatment time points (3, 6 or 12 months) features as the dependent variable with outcome at baseline (if applicable), stratification factors (service level), treatment arm and a treatment x time interaction term included as covariates. To account for correlation between repeated measures on the same individual, a subject-varying random intercept will be included. Mixed effects logistic regression can be completed using the xtmelogit command in Stata.

The secondary clinical assessments (EDSS, continuous ASIA motor and sensory scales, SCI, Paediatric quality of life, EQ5D and CSRI), with repeated measurements will also be analysed within a linear mixed model framework where generalisations of the linear mixed model will be utilised to allow for outcomes with non-normal data if necessary. Those measures with one follow up assessment will be evaluated with a general linear model. The statistical modelling will feature the outcome measure(s) as the dependent variable with corresponding baseline measure(s) (if applicable), stratification factors and treatment group featuring as covariates.

As descriptive analyses, recruitment rate, consent rate, loss to follow-up, departures from randomised treatment and the prevalence of serious adverse events (specifying deaths and ITU admissions), will be reported at 3, 6 and 12 months post-randomisation and summarized by treatment arm over the course of the

study. All causes of withdrawal from randomised treatment will be reported. Chi-squared (Fisher's exact test) will be used for categorical outcomes (e.g. serious adverse events and mortality).

All analysis will be repeated considering age status (adult or child) and putative biological markers as moderators by interaction with treatment group (control or intervention), allowing estimates of treatment effect in the sub populations to be summarized.

We will carry out further explanatory analyses to assess the efficacy of the treatment within NMO or idiopathic TM diagnosis by allowing for an interaction with treatment arm. We will explore the ICC of the sites by allowing for site as random effect in the statistical modelling.

There will be missing data in post treatment outcome variables as participants discontinue treatment or are lost to follow-up. The regression analyses are based on maximum likelihood and resulting inferences are valid provided the missing data generating mechanism is missing at random (MAR), that is missingness is predicted only by variables that are included in the model, including earlier values of the outcome variable. We will empirically assess whether any baseline variables predict missingness and should this be the case we would condition on such variables by including them in the statistical model. Sensitivity analyses will be used to assess the robustness of conclusions to missing outcome data and to departures from randomised treatment in the manner of White et al. (2011).

12.4 Futility analysis

An interim futility analysis will be conducted after 52 patients have provided a response, 26 on each treatment arm, the endpoint being a two point change in the ASIA scale at 6 months. The trial can then be terminated with the conclusion that the new treatment is no better than standard if, based on these 52 patients, the test statistic is less than zero. If sample sizes are equal, this occurs if the successes under new treatment are fewer than under standard. Otherwise, the trial proceeds to the full sample size of 170. The SAS program *two stage - interim - chi* evaluates the design deleting outcomes that would correspond to futility. The tail probabilities under the null and alternative were 0.0228 and 0.8946. The inclusion of the futility analysis therefore represents a very small loss of power.

The SAS program *two stage - stage1 - chi* evaluates the properties of the first stage of the design. It shows that the probability of abandoning the study at the interim analysis is 0.4449 under the null and 0.0201 under the alternative. Thus, there is a good chance of stopping for futility when the treatments are equivalent and a very small chance when the desired treatment effect is present (see **Appendix 5** for Futility Analysis Plan).

13. Trial Steering Committee

The TSC's key purpose will be to ensure the overall integrity of the study by monitoring its progress; investigating any serious adverse events; and taking account of regular reports from the DMEC and communication from the TMG. Ultimate responsibility for any decision required on the trial's continuation will lie with the TSC. The Committee will include an Independent Chair, Prof Richard Hughes, and a complete list

of members can be found in **section 1.6**. TSC meetings will take place at least annually and these will be arranged by the Chief Investigator and the Trial Manager in conjunction with the Chair. Increased frequency of meetings will be arranged depending on the requirements of the study DMEC and TSC recommendations.

14. Data Monitoring Committee

An independent DMEC responsible for monitoring the safety and efficacy of the study will advise the TSC of any follow up recommendations. The committee will have a DMEC chair and will consist of: one Professor of Statistics, who will be the Independent Chair and two independent Ophthalmic Surgeons. The DMEC meeting will aim to take place at least 3 weeks prior to the TSC meeting. Only the DMEC will have access to un-blinded study data, if deemed necessary. The trial statistician will provide the DMEC with an in depth report prior to each meeting and will be responsible for finalising the DMEC charter with DMEC members.

15. Study Steering Committee

The Study Steering Committee (SSC) will be responsible for monitoring the delivery of the trial on a day to day basis and will be supported and managed via the KCTU. The SSC membership will consist of: Chief Investigator, Co-Lead, Trial Manager, Data Manager, the Trial Statistician and Senior Members of KCTU. Other members of the wider research team may be invited on a meeting by meeting basis depending on the scope covered.

16. Direct Access to Source Data and Documents

The Investigators and Institutions will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing direct access to source data and other documents (eg CRFs, blood test reports, MRI reports etc).

17. Ethics & Regulatory Approvals

17.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (1996).

17.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

17.3 Approvals

The protocol, participant information sheets, informed consent forms, and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the

UK), and host institution(s) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

17.4 Reporting

Pharmacovigilance reporting and progress reports will be provided by the Chief Investigator to the REC, MHRA and funders (NIHR). At the conclusion of the trial, the CI will submit a final report to the KHP-CTO (on behalf of the Sponsor), the REC and the MHRA and the funders (NIHR), within the timelines defined in the Regulations.

17.5 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained, identifying patients by their PIN numbers and initials only. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

18. Quality Assurance

18.1 General monitoring

Monitoring of this trial will ensure compliance with Good Clinical Practice. Scientific integrity will be managed and oversight retained, by the King's Health Partners Clinical Trials Office Quality Team. The trial will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures. Regular monitoring will be performed according to ICH GCP. The investigator sites will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

18.2 Audit & Inspection

The Quality Assurance manager will conduct internal audits to check that the trial is being conducted, data recorded, analysed and accurately reported according to the protocol and in compliance with ICH GCP, meeting the requirements of the MHRA. The audits will also include laboratory activities according to an agreed audit schedule taking into consideration the 2009 MHRA guidelines for GCP in the laboratory. The internal audits will supplement the external monitoring process and will review processes not covered by the external monitor.

18.3 Serious breaches

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree a) the safety or physical or mental integrity of the subjects of the trial; or (b) the scientific value of the trial". In the event that a serious breach is suspected, the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the

Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

19. Data Handling

The Chief Investigator will act as custodian for the trial data.

Data will be managed using the InferMed MACRO database system. An electronic Case Report Form (eCRF) will be created using the InferMed MACRO system. This system is regulatory compliant (GCP, 21CRF11, EC Clinical Trial Directive). The eCRF will be created in collaboration with the trial statisticians and the CI and maintained by the King's Clinical Trials Unit. It will be hosted on a dedicated secure server within KCL.

Source data will be entered by authorised staff onto the eCRF with a full audit trail. Study sites will aim to enter eCRFs within 7 days of data collection.

Over the course of the trial, the Trial Manager will conduct on-site/central monitoring. The Data Manager/Statistician may identify data fields that should be checked against the source data during site monitoring visits, the specifics will be outlined in a Trial Monitoring Plan. Where there are data queries raised the recruiting centre staff will be responsible for resolving the queries. The Trial Manager will review responses before closing queries.

20. Data Management

Database Website Address:
https://ctumacro.iop.kcl.ac.uk/macro, also accessed via www.ctu.co.uk.

Database passwords:

Database access will be restricted to members of the research team that have been authorised and fully trained on the MACRO system, and that have been assigned personal usernames and passwords. The username and passwords will be requested by the Trial Manager from the KCTU. It is a legal requirement that passwords to the eCRF are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, training and passwords will be organised via the Trial Manger.

Data Handling & Confidentiality/Format of Records

Data will be handled, computerised and stored in accordance with the Data Protection Act,1998.

Participants will be identified on the study database using a unique code and initials. The investigator will maintain accurate patient records/results detailing observations on each patient enrolled.

Identifiable Data

All participant contact information data will be stored on spreadsheets within the recruiting site, which will have restricted access from password protected computers. Accrual data uploaded to the UKCRN portfolio

database will be anonymised and collated by the CI or delegate to the CLRN. No identifiable data will be entered on the eCRF or transferred to the KCTU.

Main Database:

SAE data will be collected on paper SAE report forms and faxed to the KHPCTO. Summary details of SAEs will be transcribed to the adverse event section of the eCRF.

For all other data collected, source data worksheets will be prepared for each patient and data will be entered onto the eCRF database via the web address above.

KCTU will provide two MACRO databases for the study:

Database 1 will be used to register patients and enter their study data from source worksheets (exam sheets/questionnaires). Researchers who need to be **blind** to treatment allocation will have access only to this database.

Database 2 will be used to collect data related to patient's therapy (IVIg, IV MP, rescue therapy). Access to this database will be restricted to individuals in the study team who are **not blinded** to the outcomes of the randomisation.

Source data worksheets will be reconciled at the end of the trial with the patient's medical notes in the recruiting centre. During the trial, critical clinical information will be written in the medical notes to ensure informed medical decisions can be made in the absence of the study team. Trial related clinical letters will be copied to the medical notes during the trial. The Principal Investigator will provide an electronic signature for each patient Case Record Form once all queries are resolved and immediately prior to database lock.

At the end of the study, essential documentation will be archived in accordance with sponsor and local requirements. The retention of study data will be the responsibility of the Chief Investigator.

Assessments/Data Collection:

Written informed consent must be obtained prior to screening and any other study specific procedures taking place.

Database lock:

The final checking of data and data cleaning will be undertaken by the trial manager, in collaboration with the investigators and trial statistician. After completion of all follow-ups and prompt entry of data, the Trial Manager will review the data and issue queries as necessary. The study site must then answer these queries before the participant's data is locked within the database. After that time, changes will not be made to the database by the research site unless specifically requested by the coordinating site in response to statistician data checks.

At the end of the trial, the site PI will review all the data for each participant and provide electronic sign-off to verify that all the data are complete and correct. At this point, all data will be formally locked for analysis. At the end of the trial, each centre will be supplied with a CD-ROM containing the eCRF data for their centre. This will be filed locally for any future audit.

21. Publication Policy

The Chief Investigator will be responsible for preparing drafts of the manuscripts, abstracts, posters, press releases and any other scientific publications arising from the study. Authors will acknowledge that the study was funded by the National Institute for Health Research. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

22. Insurance / Indemnity

In accordance with Statutory Instrument 1031 and amendments section 15 (5i.i) and the EU Clinical Trials Directive 2000/20/EC Article 3(2f), provision is to be made for: the indemnity or compensation in the event of injury or death attributable to the clinical trial: insurance or indemnity to cover the liability of the Investigator or Sponsor.

Insurance for this trial is provided by Guy's & St Thomas' Hospital NHS Foundation Trust under the Clinical Negligence Scheme for Trusts (CNST).

23. Financial Aspects

This study is funded by the National Institute for Health Research (NIHR) Health Technology Appraisal Programme (ref 11/129/148) and the Transverse Myelitis Society. Biotest AG will provide the study drugs.

24. Signatures

_____ _____

Chief Investigator Date

Print name

_____ _____

Principal Investigator (if applicable) Date

Print name

_____ _____

Statistician (if applicable) Date

Print name

25. References

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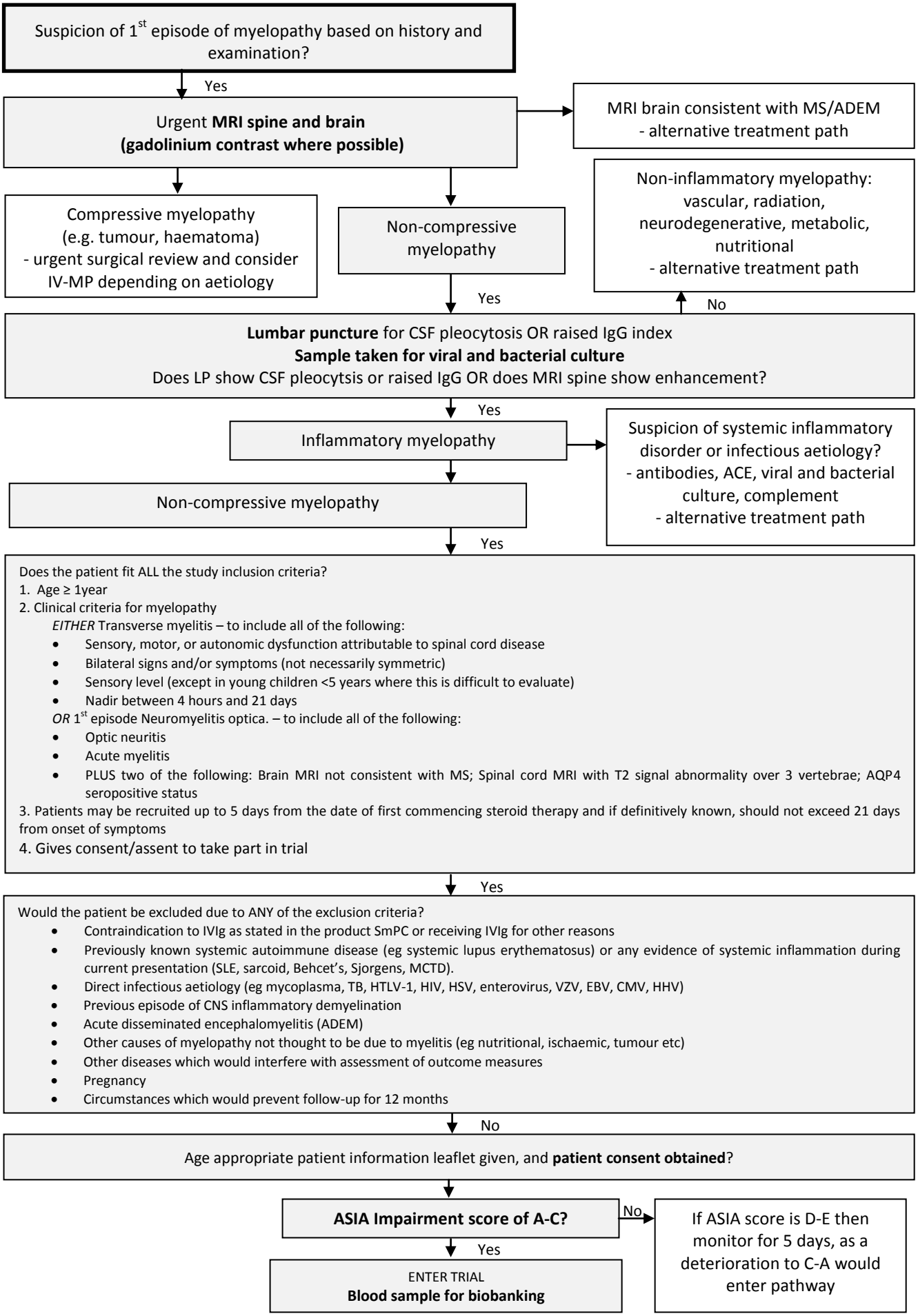
26. Appendices

26.1.1 Appendix: 1 IVIg Dosing Table

Weight (kg)	Day 1 (g)	Day 2 (g)	Day 3 (g)	Day 4 (g)	Day 5 (g)	Actual dose (g)
5.0 - 6.2	5	5				10
6.3 - 8.7	10	5				15
8.8 - 11.2	10	10				20
11.3 - 13.7	15	10				25
13.8 - 16.2	20	10				30
16.3 - 18.7	20	15				35
18.8 - 21.2	20	20				40
21.3 - 23.7	25	20				45
23.8 - 26.2	30	20				50
26.3 - 28.7	30	25				55
28.8 - 31.2	30	30				60
31.3 - 33.7	35	30				65
33.8 - 36.2	40	30				70
36.3 - 38.7	40	35				75
38.8 - 41.2	40	40				80
41.3 - 43.7	20	20	20	15	10	85
43.8 - 46.2	20	20	20	20	10	90
46.3 - 48.7	20	20	20	20	15	95
48.8 - 51.2	20	20	20	20	20	100
51.3 - 53.7	25	20	20	20	20	105
53.8 - 56.2	30	20	20	20	20	110
56.3 - 58.7	30	25	20	20	20	115
58.8 - 61.2	30	30	20	20	20	120
61.3 - 63.7	30	30	25	20	20	125
63.8 - 66.2	30	30	30	20	20	130
66.3 - 68.7	30	30	30	25	20	135
68.8 - 71.2	30	30	30	30	20	140

Weight (kg)	Day 1 (g)	Day 2 (g)	Day 3 (g)	Day 4 (g)	Day 5 (g)	Actual dose (g)
71.3 - 73.7	30	30	30	30	25	145
73.8 - 76.2	30	30	30	30	30	150
76.3 - 78.7	35	30	30	30	30	155
78.8 - 81.2	40	30	30	30	30	160
81.3 - 83.7	40	35	30	30	30	165
83.8 - 86.2	40	40	30	30	30	170
86.3 - 88.7	40	40	35	30	30	175
88.8 - 91.2	40	40	40	30	30	180
91.3 - 93.7	40	40	40	35	30	185
93.8 - 96.2	40	40	40	40	30	190
96.3 - 98.7	40	40	40	40	35	195
98.8 - 101.2	40	40	40	40	40	200
101.3 - 103.7	45	40	40	40	40	205
103.8 - 106.2	50	40	40	40	40	210
106.3 - 108.7	50	45	40	40	40	215
108.8 - 111.2	50	50	40	40	40	220
111.3 - 113.7	50	50	45	40	40	225
113.8 - 116.2	50	50	50	40	40	230
116.3 - 118.7	50	50	50	45	40	235
118.8 - 121.2	50	50	50	50	40	240
121.3 - 123.7	50	50	50	50	45	245
123.8 - 126.2	50	50	50	50	50	250
126.3 - 128.7	55	50	50	50	50	255
128.8 - 131.2	60	50	50	50	50	260

26.1.2 Appendix 2: Clinico-radiological Diagnostic Algorithm



26.1.3 Appendix 3: Trial Procedures by Visit

Patient Identification and Screening

Patients admitted to hospital with symptoms suggestive of TM should be screened for eligibility and inclusion in STRIVE study as soon as possible. A screening log should be kept at each study site. A trained member of the trial staff will screen the patient using the clinico-radiological diagnostic algorithm and suggested core study investigations, including:

- MRI of brain and spine (with gadolinium enhancement where possible)
- Lumbar puncture
- Samples for viral and bacterial culture
- Sample sent to test for AQP4 antibodies

  Results for AQP4 antibodies and viral and bacterial cultures will be pending at this stage and are not necessary for consent to take place.
- Check eligibility criteria for inclusion in STRIVE

Consent

If the patient appears eligible based on clinical presentation, the consent process can commence. Whilst the informed consent process can start at any time whilst the team is trying to establish a diagnosis, consent must be obtained before any trial related activities (such as ASIA specific exams) are performed. The trial physician will explain the trial to the patient/family and they will be given age appropriate patient information sheets (PIS) and time to make a considered decision. Staff must ensure that the patient/family can ask questions, understand they are taking part in research, what the alternatives treatments would be, the long-term commitment and that they can withdraw at any time. The clinician must be sure that all information has been understood and that consent is voluntary. Suitable patients agreeing to take part will be assented (if aged ≤ 16 years)/consented, and the process of consent also recorded in the hospital notes (to include which PIS was provided, the name of the clinician who explained the trial and took consent/assent and any relevant information). A copy of the consent/assent form should also go into the hospital notes, one copy given to the patient/family and the original kept in a separate Consent file (not with study data), along with any other identifiable information, and this file is to be kept in a secure/locked filing cabinet.

Forms required:

- Patient Information Sheets (PIS) - child/adolescent/adult/parent
- Consent/Assent forms - child/adolescent/adult

In those cases where a patient is able to provide consent to the trial orally, but is unable to sign the consent form due to paralysis, the following guidelines should be followed:

- The age appropriate PIS will be read (if necessary), and explained to the subject in the presence of a witness*.
- Once the patient has had time to consider the study, the subject can then provide oral consent and wherever possible should mark or date the ICF. This oral consent should be witnessed.
- The witness signs and personally dates the ICF to attest that the written information was accurately explained to, and apparently understood by, the subject, and that the subject gave consent freely.

*The witness will be a person who is independent of the trial and who cannot be unfairly influenced by people involved with the trial (i.e.it cannot be a member of clinical staff working directly under trial staff).

After consent, study data can officially be collected:

- ASIA Motor and Sensory scores (if patient ≥ 5 years of age) including AIS, where ASIA Impairment score of A, B or C is necessary for eligibility* (see ASIA working guideline)
- Results of pre-diagnosis tests and assessments performed as part of routine practice can be submitted as study data (including AQP4 and culture results when available).

* If the patient has an ASIA Impairment score of D or E, but may otherwise be suitable for the trial, continue to monitor – **even if a patient has commenced IV-MP treatment, they can be randomised to the trial before the end of day 5 of steroid treatment** – if the patient's ASIA score deteriorates to C, B or A during these 5 days, this would qualify as an eligible score.

Registration and Pre-Treatment (T0)

As soon as consent has been obtained the patient should be **registered** on STRIVE trial database. The database is accessible at: https://ctumacro.iop.kcl.ac.uk/macro. Access will be granted to named individuals at each site who will be listed on site's delegation log. Access (login and password details) can be obtained through the Trial Manager.

Once registration is completed the system will automatically generate a unique Patient Identification Number (PIN). This number should be noted on all patient CRF forms including site's screening log. Blood and CSF samples should be taken if possible, alongside routine samples, for the Biobank.

Pre-treatment assessments and baseline data must be collected *just prior* to randomisation and treatment allocation, at a time when IVIg is available. If the patient is admitted at the weekend, outside of pharmacy hours, then baseline measures and randomisation should take place on the Monday after, when the pharmacy can dispense IVIg.

Examinations include the Neurostatus Exam (Kurtzke's functional systems and EDSS), the EQ5D 5L or EQ5D Y (dependent on age at admission). If there was a delay between screening and randomisation, and the investigator has determined the patient's condition has worsened or improved, the ASIA Motor, Sensory and Impairment scores should be repeated to obtain a true baseline for use in primary analysis.

Forms required:

- Eligibility form
- Registration and Consent form
- Concomitant Medications form
- Neurostatus exam (Kurtzke's Functional Systems and EDSS form
- Biobank Sample form (see Biobank guideline)

Randomisation

If patients / guardians consent to take part in the study randomisation should be done as soon as possible but IVIg treatment has to be immediately available for patients randomised to treatment group.

The patient will be randomised via the King's CTU online randomisation service (https://cturandomisation.iop.kcl.ac.uk) which can only be accessed by authorised and trained trial staff. The system will generate an email to appropriate staff, allocating the patient to a treatment arm, either control or intervention, and the appropriate treatment can be initiated.

NOTE: If the patient is admitted over the weekend and cannot be randomised until Monday morning, *screening consent*, *registration and pre-treatment assessments* should go ahead as above, and treatment with IV-MP started as soon as possible. On Monday morning, the patient should be randomised; if they are allocated to the control arm, then no further treatment is added, if allocated to the intervention arm, IVIg should be added to the regime immediately.

IMPORTANT: In situations where steroid treatment has started prior to randomisation, due to late recruitment or to a delay in randomisation over a weekend, baseline ASIA impairment score must be repeated where the investigator has determined the patient's condition has worsened or improved. Investigators should indicate in patient notes that the patient is stable to account for the delay between scoring and randomisation where ASIA is not repeated.

Forms required for randomisation:

- Randomisation form

Following discharge from treatment in hospital, all primary outcome assessments at follow-up should be performed by staff blinded to treatment (see Section 9.22). Although not mandatory, secondary and tertiary outcome assessments should be performed by a blinded member of staff at follow-up where possible.

Patients can be randomised in STRIVE study **no later** than Day 5 of the start of IV MP treatment. Treatment with IVIg (if patient randomised to treatment group) should start on the day of randomisation. With these constraints, a proportion of patients will receive IVIg with IV MP on at least one day as shown in the table below.

Treatment, Rescue Therapy and Discharge (T1)

Treatment

The total study treatment period will be 5 days but if there are delays between admission and randomisation it can be extended.

Throughout the whole treatment period, the patients will be monitored daily to ensure there are no contraindications to treatment.

TREATMENT PHASE **IVMP Treatment day (D)** **IVIg Treatment day (TD)** **Study time points (T)**	D -1	D -2	D - 3	D - 4	Randomise T0 / D5 / TD1	TD 2	TD 3	TD 4	TD 5

IV MP (Control arm)	◄- - - - - - - - - - - - - - - X - - - - - - - - - - - - - - - ► (Recommended total of 5 days treatment, which can commence on day of admission (any variations from this practice will be recorded). Patients may be recruited up to 5 days from the date of commencing IV MP (D1))								
IV MP (Intervention arm)	◄- - - - - - - - - - - - - - - X - - - - - - - - - - - - - - - ► (Recommended total of 5 days treatment, which can commence on day of admission (any variations from this practice will be recorded). Patients may be recruited up to 5 days from the date of commencing IV MP (D1))								
IVIg* >41.2kg (Intervention arm)					**X**	**X**	**X**	**X**	**X**
IVIg* ≤41.2kg (Intervention arm)					**X**	**X**			

* Treatment does not need to be administered on consecutive days.

Rescue Therapy

If deemed necessary by the clinician, and there is a lack of response or deterioration, the patient will be initiated on rescue therapy such as PLEX (with the possible addition of IV-MP if necessary in the lag phase). Rescue therapy should be applied as shown in the table below. Prior to rescue therapy commencing, ASIA Motor, Sensory and Impairment scores should be taken. During the admission, any further courses of IVIg, IV-MP, or other forms of rescue therapy, should be recorded on the Rescue Therapy form.

Forms required:

- ASIA Motor, Sensory and Impairment scoring forms (see ASIA working guideline)
- Rescue Therapy form

Days on Rescue Therapy (RT)	RT Day 1	RT Day 2	RT Day 3	RT Day 4	RT Day 5	RT Day 6	RT Day 7	RT Day 8	RT Day 9	RT Day 10
Rescue Therapy										
PLEX	1-5 cycles as required and indicated by clinician									
With IV-MP **IF REQUIRED**	1-5 doses, in PLEX lag phases, if indicated by clinician									
Alternative Rescue Therapies	In line with local practice									
Rescue Therapy form										**X**
Concomitant Medications form										**X**

Please record details of the actual rescue therapy schedule used on the Rescue therapy form and ensure that the Concomitant Medication Form is also completed at the time of discharge.

Discharge

At the completion of treatment the patient will ideally be discharged but hospitalisation may be prolonged if patient suffers a relapse or deteriorates.

Forms required at the end of study treatment:

- Treatment form
- Exams/ forms required on discharge:
- Discharge form
- Concomitant Medications form
- ASIA Motor, Sensory and Impairment scoring forms (see ASIA working guideline)
- Neurostatus Examination (Kurtzke Neurological and EDSS) form
- Rescue Therapy form (if required)
- Relapse form (if required)
- Withdrawal form (if required)

Follow Up Visits (T2-T4)

The first follow-up visit can be arranged with the patient/guardian at discharge from the hospital but a reminder letter should follow nearer the time.

It is recommended that patients are invited to attend their appointment at least 30 minutes ahead of time in order to complete the questionnaires in clinic.

At the start of each follow up visit, the patient should be asked if they consent to continue with the study.

First Follow Up Visit (T2, 3 months post randomisation)

The following assessments/forms will be required:

- ASIA Motor and Sensory scales (including AIS) (see ASIA working guideline)
- Neurostatus scoring (Kurtzke's functional systems and EDSS)
- EQ-5D-Y (for patients aged 8-12 at admission/registration) *OR* EQ-5D-5L (for patients ≥13 years of age at admission/registration)
- Client Services Receipt Inventory (3 months recall)
- Study Status form
- Relapse from (if required)
- Withdrawal form (if required)

NOTE: Please provide a Stamped Addressed Envelope to patients who cannot complete the questionnaires in clinic. The questionnaires should be then completed at home and posted back to the local research team within one week of the visit.

Second Follow Up Visit (T3, 6 months post randomisation)

This is the most important study time point so every effort should be made to ensure that the patients attend their appointments. If routine blood samples are being collected at this visit, please collect a sample for

biobanking.

During this visit, the following assessments/forms will be required:

Primary endpoint

- ASIA Impairment scale component (see ASIA working guideline)

Secondary endpoints

- ASIA Motor and Sensory scales components (see ASIA working guideline)
- Neurostatus exam (Kurtzke's functional systems and EDSS)
- EQ-5D-Y (for patients aged 8-12.99 at admission/registration) *OR* EQ-5D-5L(for patients ≥13 at admission/registration)
- Individuals ≥ 13 years (at admission/registration): International SCI Quality of Life Basic Data Set
- Client Services Receipt Inventory (3 months recall)

Tertiary endpoints

- International SCI Bladder and Bowel Data Sets for patients ≥13 years (at admission/registration)
- Paediatric Quality of Life Inventory TM Parent report for Toddlers (ages 2-4 years at admission/registration) *OR* Paediatric Quality of Life Inventory TM Parent report for Young Children (ages 5-7 years at admission/registration)
- International SCI Pain Basic Data Set for individuals ≥ 13 years of age (at admission/registration) :

Additional forms to complete:

- Study Status form
- Concomitant medications form
- Biobank Sample form (see Biobank guideline)
- Relapse from (if required)
- Withdrawal form (if required)

NOTE: Please provide a Stamped Addressed Envelope to patients/guardians who cannot complete the questionnaires in clinic. The questionnaires should be then completed at home and posted back to the local research team within one week of the visit.

Third Follow Up Visit (T4, 12 months post randomisation)

At the final visit, the following assessments will be carried out:

- ASIA Motor and Sensory scales including ASIA Impairment scale (see ASIA working guideline)
- Neurostatus exam (Kurtzke's functional systems and EDSS)
- International SCI Bladder/Bowel Data Set for patients aged ≥13 years at admission/registration
- International SCI Quality of Life Basic Data Set for patients aged ≥13 years at admission/registration

- Paediatric Quality of Life Inventory TM Parent report for Toddlers (ages 2-4 years at admission/registration) *OR* Paediatric Quality of Life Inventory TM Parent report for Young Children (ages 5-7 years at admission/registration)
- EQ-5D-Y (for patients aged 8-12.99 at admission/registration) *OR* EQ-5D-5L (for patients ≥13 at admission/registration)
- International SCI Pain Basic Data Set for individuals ≥ 13 years of age (at admission/registration) Client Services Receipt Inventory (6 months recall)
- Concomitant medications form
- Study Status form
- Relapse from (if required)
- Withdrawal form (if required)

NOTE: Please provide a Stamped Addressed Envelope for patients/guardians who cannot complete the questionnaires in clinic. Completed questionnaires should be posted back to the local research team within one week of the visit.

26.1.4 Appendix 4: Common Side Effects for Intratect™

Intratect® can cause adverse reactions such as chills, headache, fever, vomiting, allergic reactions, nausea, arthralgia, low blood pressure and mild back pain, which may occur occasionally.

Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration.

Cases of reversible aseptic meningitis, isolated cases of reversible haemolytic anaemia/haemolysis and rare cases of transient cutaneous reactions, have been observed with human normal immunoglobulin.

Increase in serum creatinine level and/or acute renal failure have been observed.

Very rarely: Thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis.

Details of further spontaneously reported adverse reactions:

- Cardiac disorders: Angina pectoris (very rare)
- General disorders and administrations site conditions: Rigors (very rare)
- Immune system disorders: Anaphylactic shock (very rare), hypersensitivity (very rare)
- Investigations: Blood pressure decreased (very rare)
- Musculoskeletal and connective tissue disorders: Back pain (very rare)
- Respiratory, thoracic and mediastinal disorders: Dyspnoea NOS (very rare)
- Vascular disorders: Shock (very rare)

The adverse events reported above are expected, in the sense that they are possible known side effects of the study medication, but all reported instances of both serious and non-serious adverse events would be reported in this study. For a more detailed list of all reactions, refer to Intratect Summary of Product Characteristics (SmPC): http://www.medicines.org.uk/emc/medicine/23175/SPC/intratect/

26.1.5 Appendix 5: Futility Analysis Plan

PROPOSAL FOR AN INTERIM FUTILITY ANALYSIS

1. Introduction

Patients suffering from transverse myelitis will be randomised equally between IV immunoglobulin (the experimental arm: E) and steroids (the control arm: C). The primary analysis will concern response to treatment, defined as an improvement by two points on a paralysis assessment scale over a six month period following treatment. It is anticipated that the success rate on C will be $p_C = 0.5$. The trial is to have 90% power to achieve significance at the 0.05 level (two-sided) if the success rate on E is $p_E = 0.75$.

The final analysis of the study can be conducted in terms of the statistic $\chi^2 = \Sigma(O - E)^2/E$ which can be shown to be equal to Z^2/V where

$$Z = \frac{n_C S_E - n_E S_C}{n} = \frac{n_C n_E}{n}\left(\hat{p}_E - \hat{p}_C\right),$$

$$V = \frac{n_C n_E SF}{n^3} \approx \frac{n_C n_E \bar{p}\left(1-\bar{p}\right)}{n},$$

where n_C and n_E denote the numbers of patients and S_C and S_E the numbers of successes on C and E respectively, $n = n_C + n_E$, $S = S_C + S_E$, $F = n - S$, $\hat{p}_C = S_C/n_C$ $\hat{p}_E = S_E/n_E$ and $\bar{p} = \frac{1}{2}\left(p_C + p_E\right)$.

In fact, it will be concluded that E is significantly superior to C if $\chi = Z/\sqrt{V}$ exceeds a suitable critical value k.

For equal randomisation, we have $n_C = n_E = 0.5n$ and

$$Z = \tfrac{1}{2}\left(S_E - S_C\right) \quad \text{and} \quad V = \frac{SF}{4n}.$$

2. Sample size calculation

The SAS program `sample size - chi` concerns a trial in which 152 patients are randomised, 76 to C and 76 to E. The probability that $S_C = i$ and $S_E = j$ is found for all i, j = 0, ..., 76. Thus the probability of all 77^2 possible trial outcomes is found. The probability is found assuming that $p_C = p_E = 0.5$ and assuming that $p_C = 0.5$; $p_C = 0.75$. The possible outcomes are then arranged in descending order according to T, and cumulative probabilities of T being ≥ every possible value from 76 to −76 are computed. Reading the last row of the output for which $\chi = 1.95441$ shows that $P(\chi \geq 1.95441)$ is equal to 0.023555 when $p_C = p_E = 0.5$ and 0.90338 when $p_C = 0.5$; $p_C = 0.75$. Thus, the appropriate value for the critical value k is 1.95441. No suitable critical value can be found for n = 150, and so the sample size should be n = 152.

This exact sample size calculation depends on the control success rate being precisely 0.5, although the SAS program can be used to evaluate the decision rule – reject H_0 if $\chi \geq 1.95441$ – under any other pair of success rates. The sample size found is close to that obtained using STATA. Once the data are available, the analysis will be based on Z, allowing for any departures from the intended sample sizes of 76 on each arm. Additional patients to allow for potential drop outs can be added later.

3. An interim futility analysis

Suppose that an interim futility analysis is conducted after 52 patients have provided a response, 26 on each treatment arm. The trial is then terminated with the conclusion that E is no better than C if, based on these 52 patients, $\chi < 0$. If sample sizes are equal, this occurs id $S_E < S_C$. Otherwise, the trial proceeds to the full sample size of 152, with 76 patients on each treatment, and the null hypothesis is rejected if $\chi \geq 1.95441$.

The SAS program `two stage - chi` concerns such a design. The probability that $S_{C1} = i_1$, $S_{C2} = i_2$, $S_{E1} = j_1$ and $S_{E2} = j_2$ is found for all $i_1, j_1 = 0, ..., 26$ and all $i_2, j_2 = 0, ..., 50$, where S_{Cr} and S_{Er} are the success totals in the r^{th} stage of the trial, r = 1, 2. Thus, the probability of every possible combination of outcomes in the two stages of the trial is found. These are ordered by the final value of χ, and results for which $P(\chi \geq k) \leq 0.025$ under the null hypothesis and ≥ 0.90 under the alternative are printed out. This program takes a while to run, and produces a lot of output. Line 5031 of the output confirms that $P(\chi \geq 1.95441)$ is equal to 0.023555 when $p_C = p_E = 0.5$ and 0.90338 when $p_C = 0.5$; $p_C = 0.75$. This program is just a check.

The SAS program `two stage - interim - chi` evaluates the design, but this time outcomes in which $i_1 > j_1$ are deleted. This corresponds to stopping corresponding trials for futility. In this case $P(\chi \geq 1.95441)$ is equal to 0.022795 when $p_C = p_E = 0.5$ and 0.89462 when $p_C = 0.5$; $p_C = 0.75$. This represents a very small loss of power.

The SAS program `two stage - stage1 - chi` evaluates the properties of the first stage of the design. It shows that the probability of abandoning the study at the interim analysis is 0.44494 when $p_C = p_E = 0.5$ and 0.020060 when $p_C = 0.5$; $p_C = 0.75$. Thus, there is a good chance of stopping for futility when the treatments are equivalent and a very small chance when the desired treatment effect is present.

4. Discussion

The calculations described above indicate that a futility analysis conducted when about one third of the observations are available would be worthwhile, and would have minimal effect on the power. A final analysis conducted ignoring the interim analysis would be slightly conservative in the sense of underestimating the advantage of E over C and reporting a p-value that was bigger (and thus less significant) than any properly adjusted p-value. It would not appear to be worth making such an adjustment.

If 152 patients are recruited over two years, then 52 would be recruited after 8.2 months. The interim analysis would take place at 14.2 months, by which time a further 38 patients would have been recruited. If the analysis were instant, there would be the potential to reduce the sample size by 62 patients, although this saving would be reduced due to continued recruitment during the analysis period. If recruitment were to stretch beyond two years, the benefits of early stopping would increase.

The calculations performed in the report are qualitative, as the actual trial might depart from the model investigated here in various small ways. Here, we declare E superior to C if $\chi \geq 1.95441$, although in practice the more conventional criterion of $\chi \geq 1.960$ would probably be used. The calculations made here are exact, but only for the null hypothesis $p_C = p_E = 0.5$, and not for the more general null hypothesis $p_C = p_E$. Calculations could be rerun for the criterion $\chi \geq 1.960$, a slight increase in sample size might be needed to preserve power. In practice the sample sizes at the interim and final analyses might not be exactly 26 and 76 in each group, and they might not be equal to one another. The more general formula for χ would then be used, and this is another reason for retaining the conventional cut-off value 1.960.

Variations to the procedure, with different sample sizes at the interim and the null can be evaluated, and properties under different pairs of values p_C and p_E can be found. It would also be simple to investigate a more stringent futility criterion, requiring χ to exceed a value such as 0.5 or 1 in order to continue. This would make the loss of power more substantial, and open up the question of whether it should be compensated for by an increase in sample size.

Notice that no opportunity for stopping at the interim analysis due to strong evidence of efficacy is allowed. If that were allowed, then the properties of the method would need substantial re-evaluation and conventional analyses would no longer be conservative.

26.1.6 Appendix 6: Professional Advert

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STAGE III CLINICAL TRIAL

in acute onset **TRANSVERSE MYELITIS (TM)** or
first presentation **NEUROMYELITIS OPTICA (NMO)**

At present, we are recruiting both adult and paediatric patients, with acute onset TM or first presentation NMO to a stage III clinical trial called STRIVE, taking place in <name of Hospital>.

STRIVE is a multicentre randomi**S**ed controlled **TR**ial of **I**ntra**VE**nous immunoglobulin (IVIg) versus standard therapy for the treatment of transverse myelitis and neuromyelitis optica, with the aim to see if additional and early intervention with IVIg is beneficial.

Patients can be **included** if they:

- are aged 1 year or over
- have acute onset TM or NMO
- have and ASIA impairment score of A, B or C
- have been commenced on steroid therapy, but are randomised by day 5 of steroids
- consent to take part in the trial

They will **not be suitable** if they:

- show contraindication to IVIg or have used IVIg in the last 3 months
- have had a previous systemic autoimmune disease (eg systemic lupus erythematosus) or any evidence of systemic inflammation during current presentation.
- have direct infectious aetiology (eg varicella zoster)
- have previous episode of CNS inflammatory demyelination
- have acute disseminated encephalomyelitis (ADEM)
- have other causes of myelopathy not thought to be due to myelitis (eg nutritional, ischaemic, tumour etc.)
- have another disease which would interfere with assessment of outcome measures
- are pregnant
- have circumstances which would prevent follow-up over 12 months

What will be expected of the patient?

There will be two treatment arms:
Control Arm – standard steroid treatment with intravenous methylprednisolone
Intervention Arm - standard steroid treatment with intravenous methylprednisolone
PLUS treatment with IVIg.

Patient's recovery will be monitored at normal clinical follow up at 3, 6 and 12 months.

Patients can be recruited to the study up to 21 days from onset of symptoms if definitively known, and if the patient is already in a hospital setting, they may still be recruited up to days 5 of commencing steroid therapy.

If you come in contact with a suitable patient and you think they may be interested in taking part in this trial, please contact **<name/number>** to discuss a possible rapid referral.

Trial staff will be at hand to discuss the study, the treatment and the required follow up with the patients and their family, and will provide them with patient information sheets to help them make their decision.

Recruitment is running from November 2014 to May 2017

26.1.7 Appendix 7: Summary of Protocol Amendments

Version 4.0 (30/06/2015) to version 5.0 (27/11/2015)

The protocol was updated based on sponsor feedback in correspondence with a substantial amendment application to NRES submitted 22/12/2015.

- Wording throughout protocol amended to reflect sponsor requirement for ASIA assessment completed after consent and prior to randomization
- Wording throughout protocol amended to clarify that guidance on IV-MP dosing and MRI reporting is recommended and local variation in practice allowed
- Section 1.7 Paediatric site in Edinburgh added
- Section 6.5 IVIg dosing guidance amended to remove requirement for dosing over consecutive days
- Section 9.3 Biobanking guidance updated to allow for use of retrospective collection of bloods and CSF
- Section 23.0 Additional funding provided by charity partner, Transverse Myelitis Society

Version 3.0 (15/01/2015) to version 4.0 (30/06/2015)

The protocol was reviewed for consistency and edited to streamline content and clarify aspects of the trial procedures which were unclear based on investigator feedback. The protocol was updated in correspondence with a substantial amendment application to NRES on 09/07/2015.

- Section 1.2 Clinicaltrials.gov and HTA funding references added
- Section 1.5 Dr Mike Pike (Oxford) replaced with Dr Kate Lamb, he has retired and will no longer be collaborator, and Trial Managers details updated
- Section 1.7 Trust names corrected for minor typos
- Section 8.0 Sub-sections on patient registration and randomisation deleted as already described in section 9 and 12
- Section 9.0 Text in this section edited to avoid repetition of procedures described in Appendix 3
- Section 9.1 Study flow chart amended
- Section 9.2 Section on blinding added for clarity
- Section 10.3 Scales and Training moved from Section 9.0
- Section 24.0 PI signature section added per Sponsor requirements
- Section 25.0 References corrected
- Appendix 3 Trial Procedures by Visit updated for readability and text from Section 9.0 incorporated
- Appendix 7 Summary of Protocol Amendments added

Version 2.1 (15/10/2014) to version 3.0 (15/01/2015)

The protocol was edited to add some practical details for the conduct of the study and overall readability. An additional NHS trust was added to the study site list which required a substantial amendment application to NRES submitted 16/01/2015.

- Section 1.2 ISRCTN registration added
- Section 1.5 Contact details for Caroline Murphy, Joanna Kelly and trial manager updated
- Section 1.7 Salford Royal NHS Foundation Trust added to Manchester sites
- Section 2.0 and 6.0 Endpoints edited for clarity, Exclusion criteria “Pregnancy” changed to “Known Pregnancy”
- Section 7.0 Trial Medication updated to specify that IMP is handled in pharmacy as per standard clinical practice and according to local arrangements
- Section 8.4 and 8.5 MACRO CRF and Randomisation system processes described in more detail.
- Section 9.0 Trial Procedures, schedule and treatment charts updated for clarity. Screening and Consent process, timepoints and assessments described in more detail.
- Section 10.1 Efficacy Parameters shortened due to repetition
- Section 20.0 Database Management, description of two MACRO databases added (MACRO1 for those unblinded and MACRO2 for those blinded to treatment)
- Appendix 3 Trial Procedures by Visit, updated for readability

Version 2.0 (30/09/2014) to version 2.1 (15/10/2014)

The protocol was edited to incorporate changes requested by the ethics committee for resubmission on 28/10/2014. Details below.

- Section 1.2 REC Reference added
- Section 11.1.1. Edited to clarify that unplanned pregnancy will reported via the SAE route (not as an IME)
- Section 11.1.2 KHP-CTO will be reporting all SAEs, SARs and SUSARs to the Chief Investigator only and not to the Kings CTU as stated in V2.0
- Section 11.2 Added a sentence to say that “All adverse events will be recorded”
- Appendix 2: diagnostic algorithm “Suspicion of systemic inflammatory disorder or inflammatory aetiology” changed to infectious aetiology

Version 1.7 (28/05/2014) to version 2.0 (30/09/2014)

Substantial changes to the protocol for ethics application to NRES on 06/10/2014. Investigator and committee details and study procedures edited for clarity. Details below.

- Section 1.2 EudraCT Number added
- Section 1.3 Sponsor contact details updated
- Section 1.5 Additional co-investigators added: Prof Gavin Giovannoni (Barts), Dr Jackie Palace (Oxford), Dr Mike Pike (Oxford), Prof Paul McCrone (KCL), Dr Peter Brex (KCH), Dr Olga Cirrarelli (UCL), Prof Andrew Pickles (KCL), Ms Caroline Murphy (KCL), Ms Joanna Kelly (KCL). IMP supplier, Biotest, contact updated
- Section 1.6 Dr Mark Sanders (Clinician) added to TSC, Alasdair Parker (Clinician) added to DMEC
- Section 1.7 Study site hospital trust details updated, King’s College Hospital added as an additional site
- Section 2 Description of ‘Endpoints’ edited for clarity; Eligibility Criteria, Exclusion Criteria, IMP Dosage and Administration and Maximum Duration Of Treatment sections updated
- Section 7.3 IMP Risks added
- Section 7.6 Concomitant Medication edited
- Section 8.4 Patient Identification updated to describe eCRF system design
- Section 9.1 Study Flowchart updated with additional study forms
- Section 9.2 [Treatment] By Visit summarised and Appendix 3 added to describe treatment in more detail
- Section 9.3 Scales and Training added
- Section 9.4 Laboratory Tests updated to describe samples for bio-banking in more detail
- Section 9.5 MRI Sequences added to describe routine diagnostic process for diagnosing TM
- Section 11 Assessment of Safety updated to describe adverse event reporting in line with King’s Health Partner Clinical Trials Office procedures
- Section 13-15 Committee groups sections updated to description of key purpose and responsibilities
- Section 22 Insurance and Indemnity statement updated
- Appendices: Consent Form and Patient Information Sheets deleted, Appendix 2: Clinico-radiological Diagnostic Algorithm added, Appendix 3: Trial Procedures by Visit updated, Appendix 6: Professional Advert added