BMJ Open

Protocol for a multicentre randomiSed controlled TRial of IntraVEnous immunoglobulin versus standard therapy for the treatment of transverse myelitis in adults and children (STRIVE)

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008312
Article Type:	Protocol
Date Submitted by the Author:	25-Mar-2015
Complete List of Authors:	Absoud, Michael; Evelina London Children's Hospital at St Thomas' Hospital, Children's Neurosciences Gadian, Jonathan; Evelina London Children's Hospital at St Thomas' Hospital, Children's Neurosciences Hellier, Jennifer; King's College London, Department of Biostatistics, Institute of Psychiatry, Psychology and Neuroscience Brex, Peter; King's Health Partners Academic Health Science Centre, Department of Neurology, King's College Hospital NHS Foundation Trust Ciccarelli, Olga; National Hospital for Neurology and Neurosurgery, Queen Square, UCL Institute of Neurology Giovannoni, Gavin; Blizard Institute, University of London and Bart's Health NHS Trust, Centre for Neuroscience and Trauma Kelly, Joanna; King's College London, King's Clinial Trials Unit McCrone, Paul; King's College London, Centre for the Economics of Mental and Physical Health, Institute of Psychiatry Murphy, Caroline; King's College London, King's Clinial Trials Unit Palace, Jacqueline; John Radcliffe Hospital, Clinical Neurology Pickles, Andrew; King's College London, Department of Biostatistics, Institute of Psychiatry, Psychology and Neuroscience Pike, Michael; Oxford University Hospitals NHS Trust, Department of Paediatric Neurology Robertson, Neil; Cardiff University and Cardiff and Vale NHS Trust, Institute of Psychological Medicine and Clinical Neurosciences Jacob, Anu; The Walton Centre NHS Foundation Trust, The Walton Centre Lim, Ming; Evelina London Children's Hospital at St Thomas' Hospital, Children's Neurosciences
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Medical management, Paediatrics, Immunology (including allergy), Health economics, Research methods
Keywords:	HEALTH ECONOMICS, IMMUNOLOGY, NEUROLOGY, Paediatric neurology < PAEDIATRICS, STATISTICS & RESEARCH METHODS, Clinical trials < THERAPEUTICS

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Co-Authors: Absoud M*[1], Gadian J*[1], Hellier J[2], Brex PA[3], Cirrarelli O[4], Giovannoni G[5], Kelly J[6], McCrone P[7], Murphy C[6], Palace J[8], Pickles A[2], Pike M[9], Robertson N[10], Jacob A[11], Lim M[1].

* Joint first authors

Corresponding Author: Dr Ming Lim

Address of Corresponding Author: Children's Neurosciences, Evelina Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, King's Health Partners Academic Health Science Centre, Westminster Bridge Road, London, SE1 7EH. ming.lim@gstt.nhs.uk
Phone: 0044 2071884002 Fax: 0044 2071884269

Addresses of Co-authors:

1. Children's Neurosciences, Evelina Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, King's Health Partners Academic Health Science Centre, London (ML, MA, JG).
2. Department of Biostatistics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London (JH, AP).
3. Department of Neurology, King's College Hospital NHS Foundation Trust, King's Health Partners Academic Health Science Centre, London (PB).
4. UCL Institute of Neurology, Queen Square, London (OC).
5. Centre for Neuroscience and Trauma, Blizard Institute, University of London and Bart's Health NHS Trust, London (GG).
6. King's Clinical Trials Unit, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London (JK, CM).
7. Centre for the Economics of Mental and Physical Health, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London (PM).
8. Department of Neurology, Oxford University Hospitals NHS Trust, Oxford (JP).

9. Department of Paediatric Neurology, Oxford University Hospitals NHS Trust, Oxford (MP).

10. Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University and Cardiff and Vale NHS Trust, Cardiff (NR).

11. The Walton Centre, Walton Centre NHS Foundation Trust, Liverpool (AJ).

Keywords (max 5): immunoglobulins, intravenous; myelitis, transverse; neuromyelitis optica; randomised controlled trial; clinical trials unit.

Word Count: 3890

Number of Figures: 1

Number of Tables: 1

Number of References: 24

Number of Supplementary Files: 4

ABSTRACT

Introduction

Transverse myelitis (TM) is an immune-mediated disorder of the spinal cord which causes motor and sensory disturbance, and limited recovery in 50% of patients. Standard treatment is steroids, and patients with more severe disease appear to respond to plasma exchange (PLEX). Intravenous immunoglobulin (IVIG) has also been used as an adjunct to steroids, but evidence is lacking. We propose the first randomised control trial in adults and children, to determine the benefit of additional treatment with IVIG.

Methods and analysis

170 adults and children aged over 1 year with acute first episode TM or neuromyelitis optica (with myelitis) will be recruited over a 2.5 year period and followed-up for 12 months. Participants randomised to the control arm will receive standard therapy of intravenous methylprednisolone (IVMP). The intervention arm will receive the above standard therapy, plus additional IVIG (total dose 2g/kg).

Primary outcome will be a 2 point improvement on the American Spinal Injury Association (ASIA) Impairment scale at 6 months post-randomisation by blinded assessors. Additional secondary and tertiary outcome measures will be collected: ASIA motor and sensory scales, Kurtzke expanded disability status scale, International Spinal Cord Injury (SCI) Bladder/Bowel Data Set, Client Services Receipt Index, Pediatric Quality of Life Inventory, EQ-5D, SCI Pain and SCI Quality of Life Data Sets. Biological samples will be biobanked for future studies. Health economics analysis will be performed to calculate cost-effectiveness. After 6 months recruitment there is a planned futility analysis.

Ethics and Dissemination

Research Ethics Committee Approval was obtained: 14/SC/1329. Current protocol: v3.0 (15/01/2015). Study findings will be published in peer reviewed journals.

Registration and Funding

This study is registered with EudraCT (REF: 2014-002335-34); and ISRCTN (REF: 12127581). This project is funded by the National Institute for Health Research, Health Technology Assessment (project number 11/129/148). IVIG will be provided by Biotest AG.

Strengths and limitations of this study

- The first randomised multi-centre UK trial in children and adults with TM/NMO, recruiting 170 patients over 2.5 years with a 12 month follow-up period.
- Outcome measures will include motor, sensory, functional and quality of life measurements by blinded assessors.
- Health economics analysis will include health and social care costs.
- Findings may inform treatment decisions in other rare, inflammatory CNS disorders.
- High recruitment rate required due to low incidence of condition.

INTRODUCTION

Transverse myelitis (TM) is a rare inflammatory disorder of the spinal cord affecting approximately 350 children and adults annually in the UK.[1, 2] Histologically TM is characterised by spinal cord immune cellular infiltration, and pathogenesis is mediated by a variety of immunological mechanisms.[3] Clinical features include a rapid onset of motor, sensory and autonomic dysfunction; and a prolonged recovery phase which may continue for up to four years.[4] Diagnostic criteria for TM, were established by the TM Consortium Working Group in 2002, to distinguish TM from other conditions including MS and clinically isolated syndrome.[5] A proportion of patients initially diagnosed with TM will subsequently relapse, often with involvement of other parts of the central nervous system and may often be diagnosed with either multiple sclerosis (MS) or neuromyelitis-optica (NMO). However, a proportion of patients remain as relapsing transverse myelitis of as yet unknown aetiologies.

NMO is a relapsing subset of TM, caused by antibodies to aquaporin-4, an astrocytic water channel.[6] Clinically, patients have predominantly recurrent episodes of myelitis and optic neuritis. Initial presentation may be with myelitis alone, making it clinically and radiologically indistinguishable from TM, and patients are thus subjected to the same acute therapeutic strategies.

The American Spinal Injury Association (ASIA) international standards for neurological classification of spinal cord injury enables a standardised assessment of neurological outcome, where A is no sensory or motor function in S4-5, and E is normal function.[7] Retrospective data from paediatric cohorts suggest that 30% have ASIA A-C or expanded disability status scale (EDSS) ≥4 after TM,[8] and a retrospective French multicentre study in adults, found that 36% had a poor prognosis as defined by death or non-ambulatory status with current therapy.[9] Since this is primarily a disease of younger people, this results in significant cumulative demands on health and social care resources.

There are no robust controlled trials in children or adults to inform on the optimal treatment of TM. Standard treatment with intravenous methylprednisolone (IVMP) is based on class IV evidence that it shortens relapse duration and speeds recovery in exacerbations of adult multiple sclerosis.[6, 10-12] Given the disease severity and poor outcomes, plasma exchange

(PLEX) has been used in addition to standard therapy. Addition of PLEX showed benefit in two studies: a retrospective analysis of 122 adults with TM;[10] and a small randomised controlled trial (RCT) in adults with steroid unresponsive acute central nervous system (CNS) demyelination which included 4 patients with TM.[13] However, PLEX is not universally available in the NHS, particularly at short notice and on weekends, and can be technically difficult and costly to administer.[14]

Randomised controlled trials have demonstrated IVIG efficacy in a number of neurological conditions.[15] In steroid-unresponsive CNS demyelination IVIG is often used, although supporting data is limited to small case series and single case reports.[16, 17] IVIG appears to inhibit complement binding, neutralise pathogenic cytokines, down-regulate antibody production, enhance remyelination, and modulate phagocytosis and T-cell function.[18] The majority of these factors are common across inflammatory disorders of the CNS including TM,[19] providing a strong rationale for its use. The availability, ease of administration, familiarity and safety also make IVIG an attractive option in the acute setting.

Trial Objectives and Design:

This multi-centre, single blind, parallel group RCT will generate evidence to inform clinical and health economic decisions regarding IVIG use in adults and children with TM.

Primary Objective:

1. To evaluate if additional and early treatment with IVIG is of extra benefit in TM when compared to the current standard therapy of IVMP.

Secondary Objectives:

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. Biobanked 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.

METHODS

Study Setting

Treatment and follow-up will be in the participating tertiary neurology centres, and recruitment will also occur from feeder district general hospitals and rapid GP referrals. For further details on participating centres and trial registration please see Appendix 1.

Eligibility Criteria

Inclusion Criteria

Patients must satisfy all inclusion criteria to be eligible for recruitment. Patients will be eligible if all of the following apply at the time of randomisation:

1. Age 1 year or over
2. Diagnosis of EITHER acute first onset transverse myelitis (using the TM Consortium Working Group 2002 criteria[6]) – patients must fulfil all of the following criteria:
    i. Sensory, motor, or autonomic dysfunction attributable to spinal cord disease
    ii. Bilateral signs and/or symptoms (not necessarily symmetric)
    iii. Sensory level (except in young children <5 years where this is difficult to evaluate)
    iv. Lack of MRI brain criteria consistent with multiple sclerosis[20]
    v. Progression to nadir between 4 h and 21 days

    OR first presentation of neuromyelitis optica (using standardised criteria[21]) – patients must fulfil both absolute criteria:
    i. Optic neuritis
    ii. Acute myelitis

    plus two out of three supportive criteria (as AQP4 is often not available acutely, only the first two supportive criteria would be applied):
    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 IgG seropositive status
3. ASIA Impairment Score of A-C
4. Randomisation to occur no later than day 5 of steroids, and, if definitely known, within 21 days from symptom onset.
5. Give assent (8-16 years)/consent to participate in the trial

Exclusion Criteria

In addition to failing to meet the inclusion criteria, exclusion criteria include any of the following.

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

Interventions

Patients randomised to the **control arm** of this study will be prescribed IVMP. Paediatric patients will receive 30mg/kg or 500mg/m^2 capped to a maximum dose of 1g/day for 5 days. Adult patients will be given 1g/day for 5 days. Clinicians may follow this with an oral steroid taper according to local practice.

Patients randomized to the **intervention arm** will receive the above standard therapy *plus* additional IVIG at a total dose of 2g/kg. Doses will be divided over 2 days (children <41.2kg) or 5 days (all other patients) and individual doses may vary slightly to minimise drug wastage and anticipate for difficult intravenous access in small children.

Treatment failure will be defined as no improvement 14 days after presentation and/or 5 days after completion of treatment, and will be documented. Rescue therapy may be initiated at this point. Given the therapeutic effect of PLEX, treatment will be standardised to comprise 5 cycles in which at least 75% of plasma volume is exchanged, with a gap of 24-48 hours between cycles. An additional course of IVMP may be given if there is a delay between the decision to start PLEX and therapy initiation, at the discretion of the treating clinician. The duration and intensity of neuro-rehabilitation input will be recorded to enable comparison between groups.

Outcome measures

Outcome measures have been selected to give a 'hard' clinical endpoint that will have clinical significance, and will be assessed at the local centre by a blinded assessor. To minimise loss to follow-up, assessments are timed to coincide with routine clinical follow-up. All outcome measures are internationally accepted scales, and the primary outcome measure is the ASIA Impairment scale, which is used to measure disability in TM.[22] A six-month time-point has been selected, as the majority of neurological recovery is likely to have occurred by this point. Additional data-points will be taken at 3 and 12 months to aid statistical analysis.

Primary Outcome Measure

1. A 2 point or greater improvement in the ASIA scale (classified A-E) at 6 months post randomisation when compared to baseline, will indicate a positive outcome

Secondary Outcome Measures

2. A change in ASIA motor scale (0-100) and sensory scale (0-112)
3. A change in Kurtzke expanded disability status scale (EDSS) with Neurostatus scoring
4. EQ-5D-Y (patients aged 8-12 years at presentation) or EQ-5D-5L (patients aged ≥13 years at presentation)
5. International SCI Quality of Life Basic Data Set (patients aged ≥13 years)
6. Client Service Receipt Inventory (CSRI)

Tertiary Outcome Measures

7. International SCI Bladder/Bowel Data Set (patients aged ≥13 years)
8. International SCI Pain Basic Data Set (patients aged ≥13 years)
9. Pediatric Quality of Life Inventory TM™ (PedsQL Parent Report for Toddlers) (patients aged 2-4 years)
10. Pediatric Quality of Life Inventory TM™ (PedsQL Parent Report for Young Children) (patients aged 5-7 years)

<<Figure 1 mono>>

Figure 1: Flow chart showing the process of patient recruitment, treatment and follow-up.

Participant Timeline

Patients will be enrolled to the study for 1 year (Table 1).

Schedule Treatment day (D) Timepoint (T)	**T0** (Screening, baseline and pre-diagnosis tests)	**T1** (Treatment and discharge)							**T2** 3M	**T3** 6M	**T4** 12M	Withdrawal
		TD 1‡	TD 2	TD 3	TD 4	TD 5	*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 – e.g. 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	**X**								**X**	**S**	**X**	
≥13 yrs EQ-5D-5L	**X**								**X**	**S**	**X**	
≥13 yrs SCI QoL Basic dataset									**X**	**S**	**X**	
CSRI									**X**	**S**	**X**	

≥13 yrs SCI Bladder										T	X	
≥13 yrs SCI Bowel										T	X	
5-7yrs Peds QL										T	X	
2-4 yrs Peds QL										T	X	
Treatment form						X						
Concomitant medications								X	X	X	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	X	X	X	X						
Study Status Form									X	X	X	
*Withdrawal form (at any time point)												X

Table 1: Timeline of trial interventions. P–primary outcome measure, S–secondary outcome measure, T–tertiary outcome measure. ‡ Treatment Day 1: IVIG treatment (if applicable) to start on the same day as randomisation. Steroids may be commenced up to 5 days prior to randomisation. *Rescue therapy, relapse and withdrawal forms may only be necessary for a small subset of patients. † Adverse events will be collected throughout the study.

Trial Duration

The project will take 3.5 years. Patient recruitment will take place over the first 30 months, and collection of data will continue until 42 months.

Sample size

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, based on available data from epidemiological studies.[2, 7] The sample

size calculation is based on the conservative assumption of no correlation between repeated measures. Under these assumptions, 76 patients per group will provide 90% power and 5% type II errors for a two-sided test. The sample size will be inflated for attrition, based on our experience and the design which minimises loss to follow up, we estimate 10% attrition. This requires recruitment of 170 patients (85 participants per arm).

The ASIA total motor score (0-100) is a secondary outcome. Stata `*sampsi*` indicates that using Analysis of Covariance 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

Recruitment Plan

TM has an estimated UK incidence of 350/year, and the study centres cover approximately half of the UK population. Assuming a recruitment rate of 39% over a period of 2.5 years we would expect to recruit 170 patients. This recruitment rate is based on a patient and public consultation within the TM society, given that patients will be admitted with a devastating weakness, and the control arm will be receiving standard intervention.

Randomisation

Prior to randomisation but after consent, site staff will register a recruit on the web-based electronic data capture system (InferMed MACRO), hosted at the King's Clinical Trials Unit (KCTU). Each will be assigned a unique study patient identification number (PIN) by the system. Once baseline assessments are complete, the trained trial staff will access KCTU randomisation system and randomise the patient at the individual level using stratified block randomisation by service type (adult or child); the block will randomly vary in size. Treatment allocation will be at a ratio of 1:1. Randomisation will occur during office hours when IVIG is available. Patients eligible for trial recruitment presenting outside of these times will be commenced immediately on IVMP, and will be randomised at the first available opportunity.

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. Staff carrying out study assessments and statistical analyses will be blinded to intervention.

Data collection methods

Kurtzke neurological examination, ASIA Impairment Score, ASIA Motor and Sensory Score and EDSS scores will be completed, together with treatment, discharge and follow-up forms (see Figure 1). All assessments should ideally be performed by the same, blinded assessor, who may be a study physician, physiotherapist or research nurse. All assessors will have successfully completed ASIA and EDSS online training modules (further information detailed in Appendix 1).

Withdrawal

Patients may withdraw at any time. All withdrawals from randomised treatment will be reported. If consent is given, any existing data or samples will be retained, and follow-up data will continue to be collected, and if not then a withdrawal form will be completed. The investigator may 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. All data will be analysed on an intention-to-treat basis.

Study Data

Data Management

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 chief investigator (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.

Database passwords

Database access will be strictly restricted through passwords to the authorised research team. The CI or delegate will request usernames and passwords 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, a personalised username and password will be requested via the CI or delegate.

Identifiable data

All participant contact information data will be stored on spreadsheets within the recruiting NHS 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. Participants will be identified on the study database using a unique code and initials. The investigator will maintain accurate patient records detailing observations on each patient enrolled.

Statistical Methods

Primary analysis

If the study continues to full recruitment analyses of effectiveness will be pragmatic, based on the intention-to-treat (ITT) sample**.** The significance level will be 5% (2 sided) for specified analyses. The estimated effect size and its precision (95% Confidence Intervals) will be presented for all outcomes. The main statistical analyses will establish the effectiveness of IVIG against standard therapy at 6 months post randomisation (see primary endpoints above). To this end linear mixed modelling (LMM) 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.

There is expected to be some missing data in the post treatment outcomes variables. The LMM analyses are based on maximum likelihood and will provide valid inferences under a missing at random (MAR) missingness mechanism

Secondary analyses

The secondary clinical assessments (EDSS, ASIA motor and sensory scales, SCI data sets, PedsQL, 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.

Exploratory moderator analyses

All analysis will be repeated considering age status (adult or child) as a moderator in interaction with treatment group (control or intervention), allowing estimates of treatment effect in the sub populations to be summarised.[23] We will carry out further explanatory analyses to assess the efficacy of the treatment within NMO or idiopathic TM diagnosis and further putative biological markers by allowing for interactions with treatment arm. When considering these moderator analyses, following established methods[24] we will centre and orthogonalise interaction terms.

Further information on the statistical analysis plan can be found in the protocol and Appendix 1.

Interim Futility Analysis

TM is a rare disease and therefore requires a multi-centre trial spanning several years, precluding recruitment to other interventional studies for this cohort. As such, an interim futility analysis will be performed after 6 months follow-up of 52 patients. If sample sizes are equal, the trial may be abandoned if the successes under the intervention treatment are fewer than under standard. The probability of abandoning the study at the interim analysis is 0.4449 if there is no difference between the treatment groups, and 0.0201 if treatment improves outcome. The primary trial statistician will remain blinded to the intervention and control group, and therefore an additional unmasked trial statistician will perform the interim analysis. The results will be reviewed by the Data Monitoring Committee who have the ability to terminate the trial prematurely.

Economic Analysis

Drug pricing data and primary care, secondary care and social care costs will be calculated as previously described. Costs will be combined with the primary outcome measure in the form of a cost-effectiveness analysis. If IVIG results in higher costs and better outcome then an incremental cost-effectiveness ratio will be generated to show the extra cost incurred to achieve an extra unit of improvement. Due to uncertainty around results, cost-effectiveness planes and cost-effectiveness acceptability curves will be used, with bootstrapping of skewed results.

Long-term cost-effectiveness over a five- and ten-year period will be calculated using a Markov model. Response to treatment will be classified, and transition probabilities between groups will be derived from the six- and twelve-month follow-up data. Costs and QALYs for each category will be derived from the trial data. As limited data will be available on long term costs, we will conduct both deterministic and probabilistic sensitivity analyses.

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

There will be missing data in post treatment outcome variables as participants discontinue treatment or are lost to follow-up. Inferences will be valid provided the missing data generating mechanism is missing at random (MAR), and is not predicted by any variables in the model that is missingness is predicted only by variables that are included in the model.

Economic Evaluation

The use of IVIG, IVMP, additional treatments and rescue PLEX will be recorded throughout the follow-up period and costed using drug pricing data from the British National Formulary and the Department of Health. Use of primary care, secondary care and social care will be recorded at three, six and twelve month follow-ups using the CSRI, and costs calculated to determine total cost for control and treatment arms.

A cost-effectiveness analysis will be performed using the primary and secondary outcome measures of improvement in ASIA scores, and secondary outcome of QALYs with EQ-5D-Y, EQ-5D-5L and CSRI. If IVIG results in higher costs and better outcome, then an incremental cost-effectiveness ratio will be generated to show the extra cost incurred to achieve an extra unit of improvement.

Data monitoring

The Data Monitoring Committee (DMC) will review effectiveness and safety data during the trial to inform their recommendations to the Trial Steering Committee (TSC). The DMC is independent from the sponsor and funders, and will consist of a statistician, clinician and clinician scientist.

Harms

Most adverse drug reactions that occur in this study, whether serious or not, will be expected treatment-related side effects as IVIG has a well-established side effect profile. Monitoring and reporting of adverse events will be performed by the site PI and research team, and will be recorded on an eCRF and uploaded to the InferMed MACRO database. Serious adverse events will be reported to the sponsor in an expedited manner, who in turn will inform the CI. The CI will assess SUSAR status. If a SUSAR is detected, the CI will work with the sponsor to report to the regulatory authorities. The CI will report to relevant ethics committees and DMC.

An independent TSC and DMC will convene every 6 months, the TSC's key purpose will be to monitor study progress and act on the recommendations of the DMC. The DMC will aim to meet 3 weeks prior to the TSC convening. Increased frequency of meetings will be arranged depending on the requirements of the study DMC and TSC recommendations.

Auditing

Monitoring of this trial will ensure compliance with Good Clinical Practice (GCP). Scientific integrity will be managed and oversight retained, by the King's Health Partners Clinical Trials Office Quality Team. 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.

ETHICS AND DISSEMINATION

Ethical and safety considerations

This trial has approved by the United Kingdom National Research Ethics Service (NRES) committee (South Central - Berkshire B; REC 14/SC/1329). Clinical trial authorisation for a Type A trial has been granted via the Medicines and Healthcare Products Regulatory Agency (MHRA) notification scheme. Written approval from the respective Research and Development (R&D) departments will be obtained for each participating site.

The CI will ensure that this study (and all subsequent approved amendments) is conducted in accordance with the principles of the Declaration of Helsinki (1996), in full conformity with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines for GCP (CPMP/ICH/135/95 July 1996), the Research Governance Framework, and the Medicines for Human Use (Clinical Trial) Regulations 2004. Pharmacovigilance will be monitored by the CI. The CI will report to the REC, MHRA and funders (NIHR) during and at the end of the trial.

All protocol modifications will be disseminated to all relevant parties.

Informed Consent

A member of the trial staff will screen the patient, and if eligible, patients will be given age appropriate patient information sheets (PIS) explaining the trial (see Appendix 2). Those wishing to participate will be consented.

Confidentiality

Only anonymised data will be entered onto the eCRF. Source data will be retained on password-protected Trust computers and in patient notes to protect patient confidentiality.

Access to Data

The CI will control access to data.

Dissemination plan

Study findings will be presented in conferences and published in peer reviewed journals.

ACKNOWLEDGEMENTS

Members of TSC (R Hughes, M Lim, A Jacobs, C Lundy, B Babcock, L Gray, M Kappler, and M Sanders) and DMC (J Zajicek, S Cotterill, and A Parker); the Transverse Myelitis society, Guthie Jackson Charitable Foundation, and UK Children's Neurological Research Campaign (UKCNRC) for early support through trial design and subsequent grant applications. We are thankful to Carla Rush and Rosemary Howe for supporting the trial group on various aspects of the application. This study is also supported by the United Kingdom Clinical Research Collaboration-registered King's Clinical Trials Unit at King's Health Partners, which is part funded by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London and the NIHR Evaluation, Trials and Studies Coordinating Centre.

Collaborating Principle Investigators: Absoud M*, Brex PA*, Constantinescu C, Duddy M, Forrest K, Galea I, Giovannoni G*, Hemingway C, Jacob A*, Jacob S, Kneen R, Lim M (Chief Investigator), Murray K, Palace J*, Pike M*, Ramesh V*, Robertson N, Rog D, Vijayakumar K, Wassmer E, te Water Naude J, West S, Whitehouse W, Williams V.
* Denotes co-authors.

Centres: Children's Neurosciences, Evelina Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, London (M.L., M.A.); Department of Neurology, Guy's and St Thomas' NHS Foundation Trust, London (V.W.); Department of Neurology, King's College Hospital NHS Foundation Trust, London (P.B.); Department of Paediatric Neurology, Great Ormond Street Hospital Foundation Trust, London (C.H.); Centre for Neuroscience and Trauma, Blizard Institute, University of London and Bart's Health NHS Trust, London (G.G.); Department of Paediatric Neurology, Alder Hey Children's Hospital NHS Foundation Trust, Liverpool (R.K.); The Walton Centre, Walton Centre NHS Foundation Trust, Liverpool (A.J.); Department of Paediatric Neurology, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford (M.P.); Department of Neurology, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford (J.P.); Department of Paediatric Neurology, Birmingham Children's Hospital NHS Foundation Trust, Birmingham (E.W.); Department of Neurology, University Hospital Birmingham NHS Trust, Birmingham (S.J.); Department of Paediatric Neurology, University Hospital of Wales, Cardiff and Vale NHS Trust, Cardiff (J.W.N.); Department of Neurology, University Hospital of Wales, Cardiff and Vale NHS Trust, Cardiff (N.R.); Department of Paediatric Neurology, North Bristol NHS

Trust, Bristol (K.V.); Department of Neurology, University Hospital Bristol NHS Foundation Trust, Bristol; Department of Paediatric Neurology, Royal Manchester Children's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester (S.W.); Department of Neurology, Salford Royal NHS Foundation Trust, Salford (D.R.); Department of Paediatric Neurology, University Southampton NHS Trust, Southampton (K.F); Department of Neurology, University Southampton NHS Trust, Southampton (I.G.); Department of Paediatric Neurology, Great Northern Children's Hospital, Newcastle Hospitals NHS Foundation Trust, Newcastle (V.R.); Department of Neurology, Newcastle Hospitals NHS Foundation Trust, Newcastle (M.D.); Department of Paediatric Neurology, Nottingham University Hospitals NHS Trust, Nottingham (W.W.); Department of Neurology, Nottingham University Hospitals NHS Trust, Nottingham (C.C.); Department of Neurology, University of Edinburgh, NHS Lothian (K.M.).

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: IVIG is provided by Biotest AG, Germany, and should any commercial opportunity arise the industrial partner has an option to an exclusive licence from the sponsor (Guy's and St Thomas' NHS Foundation Trust) and potential for a revenue sharing arrangement in the event of a commercial outcome; OC serves as consultant for Novartis, Biogen, and GE Healthcare, GG has received consultation and speaking fees from Biogen-Idec, GSK, Merck-Serono, Novartis, Genzyme-Sanofi and Synthon BV, ML has received consultation fees from CSL Behring, received travel grants from Merck Serono, and been awarded educational grants to organize meetings by Novartis, Biogen Idec, Merck Serono and Bayer, JP has performed advisory work for Biogen Idec, Merck Serono Ltd, Bayer Schering Pharma, Novartis Pharmaceuticals UK Ltd, Teva Pharmaceutical Industries Ltd, Gilenya, Ono Pharmaceutical Co Ltd, Primary i-research, Alexion, Chugai Pharma Europe, receives research support from the Merck Serono Ltd, Bayer Schering Pharma, Biogen Idec and Teva, and received conference expenses from Novartis, Merck Serono and Biogen Idec, MP has received a meeting support grant from Euroimmun; MA serves on the data safety monitoring board for a study sponsored by Neurim Pharmaceuticals and is on the editorial advisory board for the *International Journal of Language & Communication Disorders*, OC is an Associate Editor of *Neurology*, GG is on the steering committee for studies sponsored by AbbVie, Biogen-Idec, Novartis, Teva and

Roche, AJ is supported by the NHS National Specialised Commissioning Group for NMO, JP serves on the scientific advisory board for the Charcot Foundation.

PB, JG, JH, JK, CM, PM, AP and NR have no conflicts of interest to declare.

FUNDING STATEMENT

This project was funded by the National Institute for Health Research, Health Technology Assessment (project number 11/129/148), with IVIG supplied by an industrial partner, Biotest AG, Germany. Should any commercial opportunity arise the industrial partner has an option to an exclusive licence from the sponsor (Guy's and St Thomas' NHS Foundation Trust) and potential for a revenue sharing arrangement in the event of a commercial outcome.

Department of Health Disclaimer:

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Health Technology Assessment, NIHR, NHS or the Department of Health.

Authors' contribution:

The study design and protocol was conceptualised by ML, MA and AJ. All co-authors contributed significantly to the conception and design of the study, with specific additional contributions from each co-author within their area of expertise; adult clinical neurology research (PB, JP, AJ, NR), paediatric clinical neurology research (MP, MA, ML), neuroimaging (OC), immunobiology (GG, NR), trial methodology (JK, CM), statistics (JH, AP) and health economics (PM).

JG prepared the early drafts of the manuscript; and developed with input from JH, ML and MA. All authors critically reviewed all versions of the manuscripts, and approved the final version.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____3, Appendix 1
	2b	All items from the World Health Organization Trial Registration Data Set	____Appendix 1
Protocol version	3	Date and version identifier	____3, Appendix 1
Funding	4	Sources and types of financial, material, and other support	____3, 20, 21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____19_____
	5b	Name and contact information for the trial sponsor	____Appendix 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____Appendix 1
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____Appendix 1

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
	6b	Explanation for choice of comparators	5,6
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7,12,14,15
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7, Appendix 1
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7,8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8,13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8 (inpatient treatment)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9,10,11

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___11,12_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___12_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____12_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____12_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____12_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____N/A (treatment will be unblinded)
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___13, Appendix 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____13_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____13_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____14,15, Appendix 1
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____14,15_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____13,14,15,16_
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__16, Appendix 1
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____15_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____17_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____17_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____17,18____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____18_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___18, Appendix 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___18, Appendix 2
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___18, 14_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___20,21_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___18_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____18_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____2_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____18_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____Appendix 2_
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____Appendix 3_

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

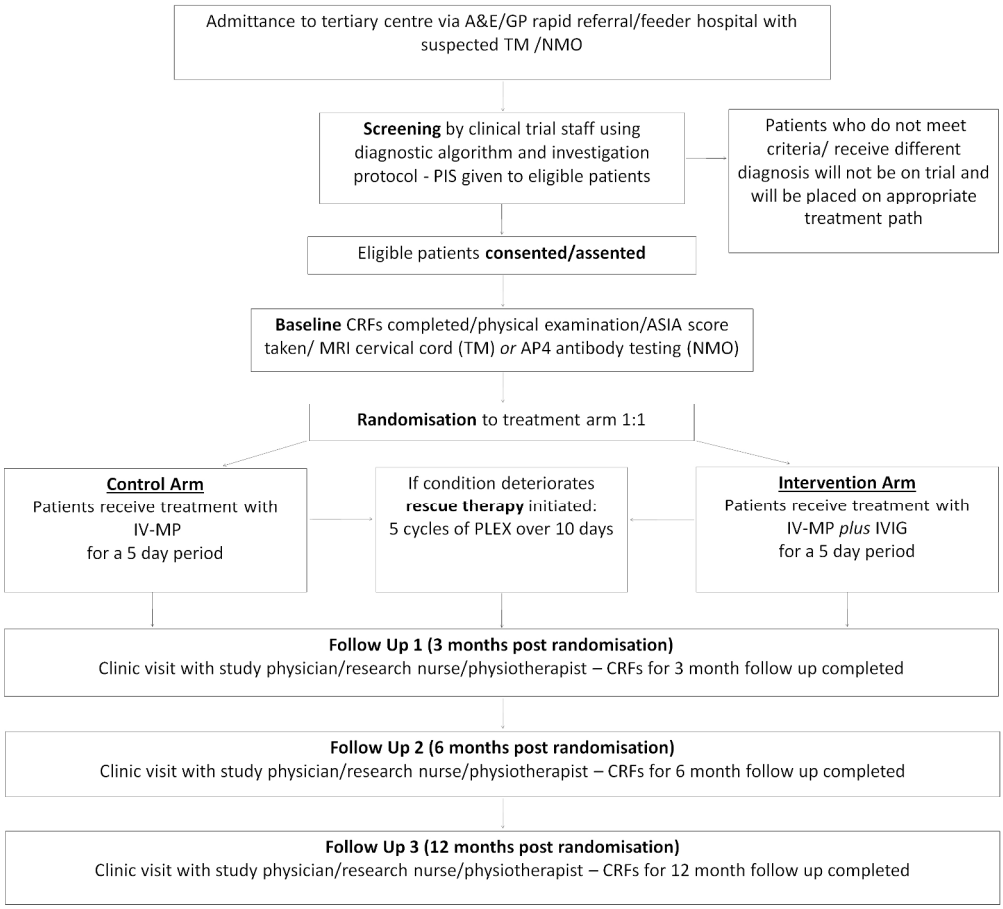


Figure 1: Flow chart showing the process of patient recruitment, treatment and follow-up.
270x243mm (300 x 300 DPI)

ADMINISTRATIVE INFORMATION

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

Trial Acronym: STRIVE

Trial Registration: This study is registered with EudraCT (REF: 2014-002335-34); and ISRCTN (REF: 12127581).

Data category	Information
Primary registry and trial identifying number	EudraCT (REF: 2014-002335-34)
Date of registration in primary registry	03/06/2014
Secondary identifying numbers	ISRCTN (REF: 12127581)
Source(s) of monetary or material support	This project was funded by the National Institute for Health Research, Health Technology Assessment (project number 11/129/148). IVIG was supplied by an industrial partner, Biotest AG, Germany.
Primary sponsor	Guy's and St Thomas' NHS Foundation Trust
Contact for public queries	Ms Rosemary Howe, Clinical Trial Manager, King's Clinical Trials Unit, IoPPN PO64 (M3.21), King's College London, De Crespigny Park, Denmark Hill, London, SE5 8AF [02078485996] [rosemary.howe@kcl.ac.uk]
Contact for scientific queries	Dr Ming Lim, Children's Neurosciences, Evelina Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, London. [02071887188] [ming.lim@gstt.nhs.uk]
Public title	STRIVE: A multicentre randomi**S**ed controlled **TR**ial of

Data category	Information
	Intra**VE**nous immunoglobulin (IVIG) versus standard therapy for the treatment of transverse myelitis in adults and children
Scientific title	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
Countries of recruitment	United Kingdom
Health condition(s) or problem(s) studied	Transverse myelitis (TM) (acute, first onset cases), including first presentation of neuromyelitis optica (NMO)
Intervention(s)	Active comparator: IVIG (2g/kg in divided daily doses) and methylpredniosolone (30mg/kg/day or 500mg/m^2/day up to 1g/day, for 5 days) Standard treatment: Methylpredniosolone (30mg/kg/day or 500mg/m^2/day up to 1g/day, for 5 days)
Key inclusion and exclusion criteria	**Ages eligible for study:** ≥1 years **Sexes eligible for study:** both **Inclusion criteria:** 1. Diagnosis of 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 MS (McDonald 2010 space criteria) • Progression to nadir between 4 h and 21 days) OR Have been diagnosed with first presentation of neuromyelitis optica.

Data category	Information
	(Patients with definite modified NMO will meet the following criteria (Wingerchuck et al, 2006). • Absolute criteria, both: i. Optic neuritis ii. 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) 2. Have an ASIA Impairment score of A, B or C 3. 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 4. Give assent(<16 years)/consent to participate in the trial **Exclusion Criteria:** 1. Contraindication to IVIg as stated in the product SmPC, or receiving IVIg for other reasons 2. Previously known systemic autoimmune disease (eg systemic lupus erythematosus) or any evidence of systemic inflammation during current presentation. 3. Direct infectious aetiology (eg varicella zoster) 4. Previous episode of CNS inflammatory demyelination 5. Acute disseminated encephalomyelitis (ADEM) 6. Other causes of myelopathy not thought to be due to myelitis (eg nutritional, ischaemic, tumour etc.) 7. Other disease which would interfere with assessment of outcome measures 8. Known pregnancy

Data category	Information
	9. Circumstances which would prevent follow-up for 12 months
Study type	Interventional Allocation: randomised Intervention model: parallel assignment Masking: single blind (investigator, outcomes assessor) Primary purpose: treatment Phase III
Date of first enrolment	March 2015
Target sample size	170
Recruitment status	Recruiting
Primary outcome(s)	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.
Key secondary outcomes	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 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

Data category	Information
	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

Protocol Version: v3.0, 15/01/2015

Funding: This project was funded by the National Institute for Health Research, Health Technology Assessment (project number 11/129/148), with IVIG supplied by an industrial partner, Biotest AG, Germany. Should any commercial opportunity arise the industrial partner has an option to an exclusive licence from the sponsor (Guy's and St Thomas' NHS Foundation Trust) and potential for a revenue sharing arrangement in the event of a commercial outcome.

Department of Health Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Health Technology Assessment, NIHR, NHS or the Department of Health.

Roles and Responsibilities:

Protocol Contributors: M Absoud, PA Brex, O Cirrarelli, G Giovannoni, J Hellier, A Jacob, J Kelly, M Lim, P McCrone, C Murphy, J Palace, A Pickles, M Pike, N Robertson; and the transverse myelitis (TM) society. Subsequent trial amendments were made following feedback from the Data Monitoring Committee (J Zajicek, S Cotterill and A Parker), Trial Steering Committee (R Hughes, M Lim, A Jacobs, C Lundy, B Babcock, L Gray, M Kappler, and M Sanders), and all Principle Investigators (M Absoud, P Brex, C Constantinescu, M Duddy, K Forrest, I Galea, G Giovannoni, C Hemingway, S Jacob, R Kneen, K Murray, J Palace, M Pike, V Ramesh, N Robertson, D Rog, K Vijayakumar, E Wassmer, J te Water Naude, S West, W Whitehouse, V Williams.)

Trial Sponsor: Guy's and St Thomas' NHS Foundation Trust.

Trial Funder: The study is funded by the National Institute for Health Research (NIHR) Health Technology Appraisal Programme (ref 11/129/148). Biotest AG will provide the study drugs.

The study sponsor and funders have not had any role in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, and do not have ultimate authority over any of these activities.

Composition, roles, and responsibilities of the coordinating centre, steering committee, data management team, and other individuals or groups overseeing the trial.

Co-ordinating Centre: Guy's and St Thomas' NHS Foundation Trust
Trial Steering Committee: Prof Richard Hughes (Honorary Chair); Ming Lim - CI and Anu Jacobs - PI (Members); Claire Lundy – Paediatric Neurologist, Barbara Babcock – TM Society, Lew Gray – TM Society, Martin Kappler – Statistician, and Mark Sanders - Clinician (Independent Members).
Data Managing and Ethics Committee (DMEC): Prof John Zajicek (Honorary Chair); Sarah Cotterill – Statistician and Alasdair Parker - Clinician (Members).

Study Centres:
We completed a pre-trial pilot to assess feasibility, variations in local practice, and margins of clinical effectiveness. The following centres have agreed to participate in this study:

Children's Neurosciences, Evelina Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, London; Department of Neurology, Guy's and St Thomas' NHS Foundation Trust, London; Department of Neurology, King's College Hospital NHS Foundation Trust, London; Department of Paediatric Neurology, Great Ormond Street Hospital Foundation Trust, London; Centre for Neuroscience and Trauma, Blizard Institute, University of London and Bart's Health NHS Trust, London; Department of Paediatric Neurology, Alder Hey Children's Hospital NHS Foundation Trust, Liverpool; The Walton Centre, Walton Centre NHS Foundation Trust, Liverpool; Department of Paediatric

Neurology, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford; Department of Neurology, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford; Department of Paediatric Neurology, Birmingham Children's Hospital NHS Foundation Trust, Birmingham; Department of Neurology, University Hospital Birmingham NHS Trust, Birmingham; Department of Paediatric Neurology, University Hospital of Wales, Cardiff and Vale NHS Trust, Cardiff; Department of Neurology, University Hospital of Wales, Cardiff and Vale NHS Trust, Cardiff; Department of Paediatric Neurology, North Bristol NHS Trust, Bristol; Department of Neurology, University Hospital Bristol NHS Foundation Trust, Bristol; Department of Paediatric Neurology, Royal Manchester Children's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester; Department of Neurology, Salford Royal NHS Foundation Trust, Salford; Department of Paediatric Neurology, University Southampton NHS Trust, Southampton; Department of Neurology, University Southampton NHS Trust, Southampton; Department of Paediatric Neurology, Great Northern Children's Hospital, Newcastle Hospitals NHS Foundation Trust, Newcastle; Department of Neurology, Newcastle Hospitals NHS Foundation Trust, Newcastle; Department of Paediatric Neurology, Nottingham University Hospitals NHS Trust, Nottingham; Department of Neurology, Nottingham University Hospitals NHS Trust, Nottingham; Department of Neurology, University of Edinburgh, NHS Lothian.

ASSESSMENT TRAINING

Assessors will be required to provide documentary evidence of satisfactory completion of training in the primary endpoint, ASIA Sensory and Motor Scoring (see: http://lms3.learnshare.com/home.aspx). In addition, assessors will be required to complete training manuals and CD's together with exam sheets for secondary outcome measures of Kurtzke's Functional Systems and Expanded Disability Status Scale which will be provided to each study site.

INTERVENTIONS

Chart detailing dosing of IVIG according to weight. Doses vary by day to minimise drug wastage.

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
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

STATISTICAL ANALYSIS

All analyses will follow the intention to treat (ITT) principle and the statistician will remain blinded. 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.[1]

A futility analysis will be undertaken after recruitment of 52 patients. If sample sizes are equal, this occurs if the successes under new treatment are fewer than under standard. The probability of abandoning the study at the interim analysis is 0.4449 if there is no difference between the treatment groups, and 0.0201 if treatment improves outcome.

If the study continues to full recruitment the final analyses of effectiveness will be conducted once the trial database has closed. 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.

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. Mixed effects logistic regression will be employed using binary outcome variable measured at the post treatment time points (3, 6 or 12 months).

The secondary clinical assessments with repeated measurements will also be analysed within a linear mixed model framework. Those measures with one follow up assessment will be evaluated with a general linear model. Stratification factors and treatment groups will feature as covariates.

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

REFERENCES:

1. White IR, Horton NJ, Carpenter J, et al. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ 2011;342:d40

Patient Information Sheet for Adults

STRIVE: A multicentre randomiSed controlled TRial of IntraVEnous immunoglobulin (IVIg) versus standard therapy for the treatment of transverse myelitis in adults and children

Invitation

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the information below carefully:
Part 1 tells you the purpose of this study and what will happen to you if you take part
Part 2 gives you more detailed information about the conduct of the study

One of our team will go through the information sheet with you and answer any questions you have, and you may talk to others about the study if you wish.

PART 1

Why have I been asked to take part?

You have been chosen because you have developed either transverse myelitis (TM) or neuromyelitis optica (NMO).

TM is a rare nervous system disorder where the coating (myelin) of nerve cells in the spinal cord become inflamed, affecting the transmission of signals along the cord. TM can also sometimes develop as part of NMO, a nervous system disorder which also affects vision. TM and NMO can affect both adults and children.

In TM, signals to the body below the inflamed area of the spinal cord can be affected producing symptoms including muscle spasms, muscle weakness and lower back pain. The person may have odd sensations of the skin and soft tissue including tingling, numbness, coldness, burning or hypersensitivity to touch. In some people, loss of bladder or bowel function and paralysis occur. In NMO, as the optic nerve can be affected, the most prominent symptom is a blurring or loss of vision. Symptoms develop over hours, days, or weeks and the causes are not well understood. They may be linked to an autoimmune response, when the immune system mistakenly attacks body tissues.

As TM and NMO are rare diseases, little is known about the causes, mechanisms and best treatment routes – it is thus important that we do more research, and this study aims to investigate what is the most effective treatment. Every child or adult in your region affected by TM or NMO will be invited to take part in this study and we hope to include 170 people.

What is the purpose of the research project?

When people suffer from an attack of TM or NMO, many recover well having maybe some muscle weakness, or poor vision in NMO. At the moment, we cannot always predict what the future holds for those affected, but we think that the sooner patients get treatment, the less damage is done to their nerves and the better their recovery. There are several treatments available, but different hospitals use different ones. We would like to investigate if a combination treatment is better than the most common standard treatment used.

We will not be using any new medicines. All are used regularly in hospitals and are already used in TM and NMO. The drugs are intravenous methylprednisolone (IV-MP) which is a corticosteroid and intravenous Immunoglobulin (IVIg), which both suppress inflammation. The study does not involve using a placebo or dummy treatment; everyone will receive the standard treatment (IV-MP), so at the very least you will receive standard care for your illness.

If after initial treatment your doctor and you think that there has not been enough improvement, different treatments such as plasma exchange (which involves replacing the plasma in your blood) may be considered.

The study aims to:

1. Find out if different treatments give different results.
2. See how these treatments affect quality of life, wellbeing, participation and behaviour over time.
3. Aid future research by collecting and storing blood and spinal fluid samples for future studies. These samples will be taken at the same time as samples which the hospital takes as part of routine investigations.
4. Ultimately, produce a treatment 'gold standard', providing a set of assessments to aid diagnosis and a tested treatment plan.

Do I have to take part?

The answer is no, it is up to you to decide whether or not to take part. Also, if you do decide to take part, you are free to withdraw from the research at any time, you do not even have to give your reasons. Whatever your decision, or even if you join but later chose to withdraw, it will not affect the standard of care you will receive. Furthermore, if for any reason you lose the capacity to consent/withdraw, you will automatically be withdrawn from the study. In all cases of withdrawal, any data or samples already collected with consent, would be retained and used in the study.

What do I have to do if I agree to take part?

The consent/assent process

Once your have read this leaflet and have had any questions answered by our research team, if you are happy to take part you will be asked to sign a consent form. You will be given a copy of the consent form plus this information sheet to keep for your records.

The care you will receive in hospital will be very similar to that of any patient with acute TM or NMO, with the addition of some extra examinations, some study questionnaires, an MRI scan and some extra blood and spinal fluid samples for storage in our Biobank.

Assessments
The doctor will perform some physical assessments and tests on you, mainly tests that all patients with TM undergo.

Clinical Data and Questionnaires
The doctor will collect information about your normal health, family history, and you current illness and its onset. There will also be some study specific forms and questionnaires to complete; this should take about 30-45 minutes.

MRI scans
MRI uses a magnet to make medical pictures of the body and it allows us to see which areas of the brain or spinal cord have inflammation. The scan is part of the care given to all patients with TM or NMO, so if you have already had a scan during this admission, the research team would like to look at a copy of this. If not, one will be arranged for you.

Bloods and Spinal Fluid Samples
A sample of your blood (via venepuncture) and your cerebrospinal fluid or CSF (via lumbar puncture) will be taken for the purpose of the study and biobanked. You will NOT undergo any *additional* procedures to obtain these samples, we will only ask for extra samples to be taken during routine hospital venepuncture/lumbar puncture. We would like you to know that:

- Blood and spinal fluid samples are taken in all cases of TM as part of routine hospital investigations.
- Your study samples will be stored in a registered Human Tissue Act licensed biobank (a secure place for future use). Further studies will ensure a high standard of research review by the study team.
- One such study may be for future DNA analysis. DNA (deoxyribonucleic acid), is found in all cells of the body, and contains the genetic information for the development and working of human beings. Analysing blood samples will allow future research to find out the relationship between our environment (exposures) and our personal susceptibility (genes). We may also come up with better diagnostic tests. If in the future we do find something interesting in analysis of the DNA, we will ask for an extra blood sample to check our findings. We will also try to repeat our findings in a clinical laboratory that undertakes genetic tests, if you would like and if this is possible. Sometimes, our findings might need more tests in the laboratory to know if they are relevant or not. Any results are research findings and are not a clinical test.

Randomisation and Treatment
Once we have collected all the above baseline information (pre-treatment information), you will be randomised to one of two treatment arms/groups. Randomisation ensures that both groups are the same to start with, so that the different treatments can be compared fairly. You have a 50% chance of going into either treatment arm.

Treatment arm 1 will receive the standard hospital treatment for demyelination, intravenous methylprednisolone (IV-MP), for a period of 5 days.

Treatment arm 2 will receive standard therapy with IV-MP for 5 days *plus* treatment with intravenous immunoglobulin (IVIg) for 5 days.

Unlike some studies, the doctors will not be 'blinded', meaning that they will know which treatment your will be receiving, and you will also be allowed to know.

Follow Up

Once treatment is complete and you have left hospital, we would like to monitor your progress. We will do this during your routine follow-ups in clinic, at 3 months, 6 months and 12 months, and it will take the form of study assessments and questionnaires. These assessments will chart your physical recovery, but clinical questionnaires will also give us information on factors such as you progress, quality of life and wellbeing. At the 6 month visit, if routine blood samples are being requested, we will also take another biobank sample. Each visit will take about 1 hour. These visits will be conducted by staff who will not know which treatment you received (so that they will be unbiased with the results of your assessment) – we will ask you not to tell the assessor which treatment arm you were on. At the last visit, we will ask whether we can contact you in the future to take part in other studies.

What are the possible disadvantages and risks of taking part?

We foresee no additional risks by taking part in the study, as all medications are already used in general practice, there are no placebos, and as a minimum, *every* patient will receive standard care given in hospitals for their illness.

If you should receive IVIg treatment, there are some common side effects, but these are transient and can occur in any patient taking IVIg, for any condition. These can include: chills, headache, fever, palpitations, nausea and vomiting, allergic reactions, infusion related reaction, low blood pressure and mild back pain or joint pain. Your doctor will talk to you further about these if you require.

During treatment on either arm of the trial, if your doctor does not think that there has been enough improvement in your condition, additional treatment with plasma exchange (PLEX) will be considered as a 'rescue therapy'. PLEX involves replacing the plasma in a person's blood. The possible use of a rescue therapy has been built into study procedure, and means that if it is required, it will not affect your study status.

What are the possible benefits of taking part?

We cannot promise that participation in this study will provide extra benefits. We do hope, however, that the information provided will help further improve treatment for people with TM in the future.

PART 2

What if there is a problem whilst I am on the study?

If you have a concern about any aspect of this study, you should ask to speak to the researchers, who will do their best to answer your questions. Please contact: <NAME>, Principal Investigator, at (insert email): XXXXX or by calling (insert telephone no) XXXXX.

If you have a complaint, you should talk to your research doctor who will do their best to answer your questions. If you remain unhappy, you can make a formal complaint through the NHS complaints procedure. Details can be obtained through the Guy's and St Thomas' Patient Advisory Liaison Service (PALS) on 0207 1887188, address: PALS, KIC, Ground floor, north wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH .
This study is insured by Guy's & St Thomas' NHS Foundation Trust under the Clinical Negligence Scheme for trials.

All professional staff involved in the study hold professional indemnity to work within Guy's and St Thomas' NHS Trust. In the event that you are harmed during the research and this is due to negligence then you may have grounds for legal action for compensation against Guy's and St Thomas NHS Trust but you may have to pay your legal costs. The normal NHS complaints mechanisms are still available to you.

Will my participation in the research project be kept confidential?

Yes. All the information about your participation in this study will be kept confidential in accordance with the Data Protection Act 1998. The information from each patient will be stored in a confidential database, where it will be identified only by a unique PIN number.

Involvement of the General Practitioner/Family doctor (GP)

Your GP will be notified of your participation in the trial, and will receive a copy of the consent form.

Will any genetic tests be done?

No specific genetic tests will be carried out.

What will happen to the results of the research study?

It is intended that the results will be published in a reputable medical journal; you will not be identified in any report/publication. The results of the study will also be presented in National and International meetings. If you would like a summary of the final results, this will also be made available.

Who is organising and funding the research?

The research is being funded by the National Institute for Health Research (NIHR.ac.uk) and is organised by a research team from the King's Clinical Trials Unit and the Evelina Children's Hospital in London, as part of the King's Health Partners Academic Health Science Centre.

Who has reviewed the study?

The study also has ethical approval from The South-Central Berkshire B Research Ethics Committee and approval from your local hospital's Research & Development Department.

If you have any questions about this study, then please contact the study team members at: <INSERT LOCAL PHONE NUMBER>

Alternatively, if you would like to discuss your participation in the study with someone outside of the study team, you may wish to approach the local Patient Advisory Liaison Service (PALS) on <*INSERT LOCAL PALS NUMBER*>.

Thank you for taking the time to read this information sheet

Information sheets for children aged 6-11

A study of the best treatment for transverse myelitis (TM

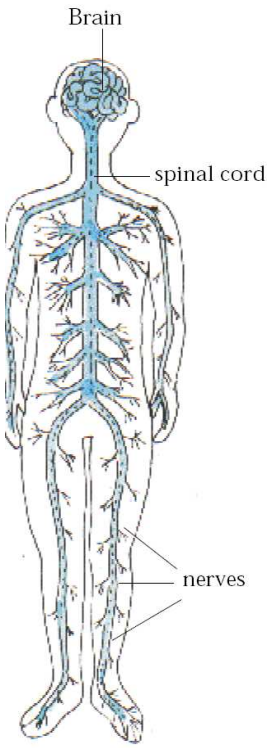
Invitation to take part

You are being invited to take part in a research study. Before you decide if you want to join in, it is important to understand why the research is being done and what it will involve for you. Read through this leaflet and then talk about it with your family, friends, doctor or nurse if you want to.

Why have I been asked to take part?

You are not feeling very well at the moment, you might have heard the doctor say transverse myelitis, but we can just call it TM, or a type of TM called neuromyelitis optica, which we can shorten to NMO. We will ask about 170 people (children and adults) with these illnesses to join in the study.

What are TM and NMO?



The brain is like a computer that sends messages to your body telling it what to do - like "walk" or "talk."

The spinal cord is like a thick bunch of wires attached to the brain. Messages travel from the brain along the spinal cord to the muscles all around your body.

Therefore, if your brain wants your arm to lift up and wave, it sends a message along your spinal cord to your arm. Your arm gets the message and starts to wave!

When a person has TM, the covering that protects the nerves in the spinal cord is affected, so the messages cannot always get through.

In TM, most of the problems are in the spinal cord. If you have TM, you may have symptoms like weak muscles or strange feelings in your skin like tingling, numbness or extreme hot or cold. You may also find it difficult to go to the toilet.

In NMO (a type of TM), the same sort of damage is happening to spinal nerves and affecting messages, but there is also a problem with eyesight.

What is research and why is this project being done?

Research is trying to find the answers to questions (or problems) by carrying out tests. There are different treatments to help make children with TM get better, but we want to find out the one that is best?

Do I have to take part?

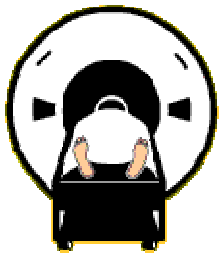
No - it is up to you. Moreover, if you do decide to take part but then change your mind later, you can tell your parents or nurse or doctor that you want to stop and you do not even have to tell us why if you do not want to. Nobody will be upset with you.

What will happen to me if I take part in the research?

If you are happy to take part, we need to get you and your parent/guardian to sign a form agreeing to take part. If you are between 8 and 11 years old, you can sign what is called an *Assent* form, whilst your parent(s) sign a *Consent* form. If you would like to take part but do not want to sign, you can just let your parent(s) sign the Consent form. If you are under 8, you do not have to sign any forms.

We will then ask you and your parents to answer some questions regarding your normal health, your family and how you feel at the moment. This will take about 45-60 minutes.

All children that come into hospital with TM need to have some examinations and tests done, and we can use these for our study.



One of these examinations will be an MRI scan, which you might have heard of. The MRI uses magnetic fields to create an image of the brain and spinal cord and shows patches of the brain that are affected by this type of illness.

Other types of tests that all hospitals have to do for TM are tests on your blood and spinal fluid. When the nurse takes these samples, we will be asking him or her to take a few extra ones at the same time for the study.

We would like to store some of these samples to use for future research.

Once we have all the information about you that we need, we will start you on one of two treatments:

- one treatment is with something we can just call IV-MP (its long name is intravenous methylprednisolone). You would be on this treatment for 5 days.

OR…

- the other treatment is with IV-MP *and* something we can call IVIg (whose long name is intravenous immunoglobulin). You would be on this treatment for up to 5 days.

These medicines (the IV-MP and IVIg) are given via a small tube into your vein called a cannula. This is the way they are usually given to patients and is not just for the study.

If you do get the IVIg, in some people it can have an effect on them, for example they can feel a bit sick, get a temperature, a headache or feel achy – let your doctor know if you get any new problems. Whichever treatment you get though, the medicines have already been used on children with TM all over the country, we are just researching which works best.

When your treatment is finished and you have left hospital, we would like to keep an eye on you to see how you are doing. We will do this by meeting you at 3, 6 and 12 months at your normal follow up appointments with the doctor. We will ask you and your parents or guardian some more questions.

All the information we collect about you will be stored safely. Nobody other than your doctor and the research team can find out about it.

Might anything about the research upset me?

If anything does worry you or you think things are not right, do not be worried about telling your parent(s) and the research team, and they will be able to help.

Will being part of this research help me?

We cannot promise being on this study will help you, but the information we get might help treat children with TM in the future. If you wish, when the study is finished, you and your parents can have a copy of the results – let us know if you would like to have these.

Thanks for reading this -
we hope you will join us in this study!

Information sheets for children aged 12-16

A study of the best treatment for transverse myelitis (TM)

Invitation

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the information below carefully:
Part 1 tells you the purpose of this study and what will happen to you if you take part
Part 2 gives you more detailed information about the conduct of the study

One of our team will go through the information sheet with you and answer any questions you have, and talk about it with your family, friends, doctor or nurse if you want to.

PART 1

Why have I been asked to take part?

You have been asked because you have developed an illness called transverse myelitis, but we can just call it TM, or you may have a form of TM called neuromyelitis optica, or NMO for short.

TM is a rare disease that affects the coating (myelin) of nerve cells in the spinal cord. Nerves are how we send messages around the body. In TM, damage is caused by inflammation (swelling) in the nerves of the spinal cord which means messages have trouble getting through. The cause may be an 'autoimmune' response - when your defence systems mistakenly start to attack your own body!

Because the messages are not getting through properly, it can produce symptoms, which can include muscle weakness and lower back pain. There may also be odd sensations such as tingling, numbness, coldness or burning or super-sensitivity to touch, or you might have problems going to the toilet. In NMO, as the nerves to the eyes can also be affected, the most noticeable symptom is a blurring or loss of vision Symptoms can develop over hours, days, or even weeks. It can affect both adults and children.

As TM is a rare disease, it is important that we do more research. Every child in your region affected by TM will be invited to take part in this study and we hope to include 170 children and adults.

What is the purpose of the research project?

Whilst many children with TM make a good recovery, some will be left with ongoing health care problems – we cannot always predict what will happen. We think that the sooner patients get treatment; the less damage is done to their nerves and the better their recovery. At the moment, different hospitals give different treatments, and we would like to investigate if there is one that works best.

We will not be using any new medicines, all are used regularly in hospitals and they are all already used in children with TM. One is called methylprednisolone (IV-MP) and one is an immunoglobulin (IVIg), and again we will just call them IV-MP and IVIg. Both of these medicines work to stop the swelling (inflammation) that affects the nerves. We would also like you to know that *every* child on the study will receive the standard initial treatment given in hospitals for these conditions, so there is no risk that you will do less well if you do take part.

We are asking if you would agree to take part in a research project and help to:

1. Find out if different treatments give different results.
2. See how these treatments affect children's quality of life, schooling, participation and behaviour over time?
3. Help in future studies - investigating for example why these illnesses occur, if we can predict them etc. - by letting us store some of your blood and spinal fluid for future studies. These samples will be taken at the same time as samples which the hospital takes as part of its normal investigations.
4. Ultimately, provide a 'gold standard' of treatment to guide all doctors, so that they can use it on children like you, knowing that they are giving the best care.

Do I have to take part?

No you do not – it is completely up to you! Ask the doctor or research staff, if you have any questions that are troubling you. And if you do decide to take part, **you are still free to stop taking part at any time during the research without giving a reason.** If you decide not to take part, or if you decide to stop at any time, this will not affect the care you receive.

What will happen to me if I take part?

The consent/assent process

If you are happy to take part, and are happy with the explanations from your research team and family, the first thing you and your parent/guardian will be asked to do is to give your consent – you can sign an Assent form and your parent(s) sign a Consent form. If you would like to take part but do not want to sign, you can just let your parent(s) sign the Consent form. You will be given a copy of this information sheet and your signed form to keep.

What will I be asked to do next?

Assessments

The doctor will do some assessment and tests on you, or he may already have performed these in which case we will just use the results. These will mainly be tests that all patients with demyelinating diseases undergo.

Questions about your illness

We will ask you and your parents/guardian to answer questions about your family history,

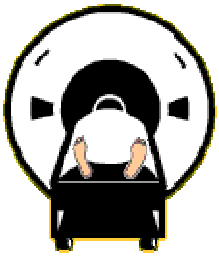
your health normally how you are feeling at the moment, and there will be some paper based assessments to complete. This will take about 45 minutes.

Bloods and Spinal Fluid

Before your start your treatment, and during your stay, the hospital will need to take samples of your blood and spinal fluid. When they take these samples, we will be asking them to take a few extra ones for the study, and we will keep these safe in a 'biobank' for future research.

MRI scans

Children with TM undergo an MRI scan as part of their investigation. The MRI uses magnetic fields to create an image of the brain and spinal cord and shows patches of the brain that are affected. The scan is part of the care given to children with TM – if you have already had a scan during this hospital visit, the research team would like to look at this scan.



Randomisation and Treatment

When we have collected all the pre-treatment information you will be randomised, (like flipping a coin), to one of two treatment groups. Randomisation ensures that both groups are the same to start with, so that the different treatments can be compared fairly. You have a 50% chance of going into either treatment group.

Treatment group 1 – the patient receives the standard hospital treatment for TM, which is IV-MP for 5 days.

Treatment group 2 – the patient receives standard therapy with IV-MP for 5 days *plus* treatment with IVIg for up to 5 days.

These medicines (the IV-MP and IVIg) are given via a small tube into your vein called a cannula. This is the way they are usually given to patients and is not just for the study.

Follow up

When your treatment is complete, we would like to monitor your progress. We will do one assessment before you leave hospital, but we would also see you at your routine follow-ups in clinic, at 3 months, 6 months and 12 months. At these clinic visits we will go through some assessments with you and also ask you to complete some questionnaires. At the 6 month visit, if routine blood samples are being requested, we will also take one more sample for the biobank. Each study visit will take about 45-60 minutes and will be carried out by someone who will not know which treatment you received (this is so they can be unbiased about the results of the assessments) – we will ask you not to tell them! On the last visit, we will ask whether we can contact you in the future to take part in other studies.

All your information will be stored in a confidential (private) database. The database is anonymous and will not have your name or personal details on it; instead you will be identified by a unique study number. Information on each patient will be updated during each clinic visit over the study period.

What are the possible risks benefits of taking part?

There are no extra risks if you take part in the study, and at the very least you will receive standard care for your illness. If you should receive IVIg treatment, there are some common side effects, but these are temporary and can occur in any patient taking IVIg, for any condition. These can include: chills, headache, fever, nausea and vomiting, allergic

reactions, palpitations, low blood pressure and mild back pain or joint pain. The doctor will talk to you further about this if you require.

During treatment, if your doctor does not think that there has been enough improvement in your condition, additional treatment with plasma exchange (PLEX) will be considered as a 'rescue therapy'. PLEX involves replacing some important components of a person's blood.

We cannot promise the study will provide extra benefits. We do hope, however, that the information you provide will help further improve treatment for young people with acute TM in the future. If you wish, when the study is finished, you and your parents can have a copy of the results – let us know if you would like to have these.

PART 2

What if there is a problem or something goes wrong?

If you have any worries or complaints during the study, you should share this with your parent(s) and the research team. Your parent(s) have been given details of who to call or how you could make a complaint in their Parent Information Sheets.

Will anyone else know I am doing this?

Yes, some people from the research team will see your medical notes to make sure the research is being done properly, and your family doctor will be told you are taking part.

Who is organising and funding the research?

The National Institute for Health Research is funding the research and it is being organised by a research team from the Evelina Children's Hospital in London.

Who has reviewed the study?

The study has been reviewed independently by expert panels and has been checked by an Ethics Committee, as is all research; they make sure that the research is OK to do. This study has been checked by the South-Central Berkshire B Research Ethics Committee.

How can I find out more?

You can ask members of the research team questions, you can speak to your parent/guardian or you can look at the study website: www.****.org.uk or phone us on *******.

If you would like to discuss your participation in the study with someone outside of the study team you may wish to approach the local Patient Advisory Liaison Service (PALS) on <*Insert local PALS number*>.

Thank you for reading this – please ask any questions if you need to.

Information sheets for parents/guardians

STRIVE: A multicentre randomiSed controlled TRial of IntraVEnous immunoglobulin (IVIg) versus standard therapy for the treatment of transverse myelitis in adults and children

Invitation

You and your child are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the information below carefully:
Part 1 tells you the purpose of this study and what will happen to you if you take part
Part 2 gives you more detailed information about the conduct of the study

One of our team will go through the information sheet with you and answer any questions you have, and you may talk to others about the study if you wish.

PART 1

Why has my child been asked to take part?

Your child has been chosen because he/she has developed either transverse myelitis (TM) or neuromyelitis optica (NMO).

TM is a rare nervous system disorder where the coating (myelin) of nerve cells in the spinal cord become inflamed, affecting the transmission of signals along the cord. TM can also sometimes develop as part of NMO, a nervous system disorder which also affects vision. TM and NMO can affect both adults and children.

In TM, signals to the body below the inflamed area of the spinal cord can be affected producing symptoms including muscle spasms, muscle weakness and lower back pain. The person may have odd sensations of the skin and soft tissue including tingling, numbness, coldness, burning or hypersensitivity to touch. In some people, loss of bladder or bowel function and paralysis occur. In NMO, as the optic nerve is affected, the most prominent symptom is a blurring or loss of vision. Symptoms develop over hours, days, or weeks and the causes are not well understood. They may be linked to an autoimmune response, when the immune system mistakenly attacks body tissues.

As TM and NMO are rare diseases, little is known about the causes, mechanisms and best treatment routes – it is thus important that we do more research, and this study aims to investigate what is the most effective treatment. Every child or adult in your region affected by TM or NMO will be invited to take part in this study and we hope to include 170 people.

What is the purpose of the research project?

When people suffer from an attack of TM or NMO, many recover well, having maybe some muscle weakness, and in NMO poor vision. At the moment, we cannot always predict what the future holds for those affected, but we think that the sooner patients get treatment, the less damage is done to their nerves and the better their recovery. There are several treatments available, but different hospitals use different ones. We would like to investigate if a combination treatment is better than the most common standard treatment used.

We will not be using any new medicines. All are used regularly in hospitals and are already used in TM and NMO. The drugs are intravenous methylprednisolone (IV-MP), a corticosteroid and intravenous Immunoglobulin (IVIg), which both suppress inflammation. The study does not involve using a placebo or dummy treatment; everyone will receive the standard treatment (IV-MP), so at the very least your child will receive standard care for their illness.

If after initial treatment your doctor and you think that there has not been enough improvement, different treatments such as plasma exchange (which involves replacing the plasma in a person's blood) may also be considered.

The study aims to:

1. Find out if different treatments give different results.
2. See how these treatments affect children's quality of life, schooling, participation and behavior over time?
3. Aid future research by collecting and storing blood and spinal fluid samples for future studies. These samples will be taken at the same time as samples which the hospital takes as part of routine investigations.
4. Ultimately, produce a treatment 'gold standard', providing a set of assessments to aid diagnosis and a tested treatment plan.

Does my child have to take part?

The answer is no, it is up to you - and whenever possible your child - to decide whether to take part. You are both free to withdraw from the research at any time, you do not even have to give your reasons. Whatever your decision, or even if you join but later chose to withdraw, it will not affect the standard of care your child will receive. Furthermore, if a child is on the study but the parent/guardian loses the capacity to consent/withdraw, the patient would automatically be withdrawn from the study. In all cases of withdrawal, any data or samples already collected with consent, would be retained and used in the study.

What does my child have to do if we agree to take part?

The consent/assent process

Once your have read this leaflet and have had any questions answered by our research team, if you are happy to take part you will be asked to sign a consent form. If your child is between 8 and 16, is able to understand the research and is happy to take part, they can also sign an "assent" form at the same time. You will be given a copy of your consent/assent forms plus this information sheet to keep for your records.

The care your child will receive in hospital will be very similar to that of any child with acute TM or NMO, with the addition of some extra examinations, some study questionnaires, an MRI scan and some extra blood and spinal fluid samples for storage in our Biobank.

Assessments
The doctor will perform some physical assessments and tests on your child, mainly tests that all patients with TM undergo.

Clinical Data and Questionnaires
The doctor will collect information about your child's normal health, family history, and their current illness and its onset. There will also be some study specific forms and questionnaires to complete; this should take about 30-45 minutes.

MRI scans
MRI uses a magnet to make medical pictures of the body and it allows us to see which areas of the brain or spinal cord have inflammation. The scan is part of the care given to all patients with TM or NMO, so if your child has already had a scan during this admission, the research team would like to look at a copy of this. If a scan has not already been taken, we will arrange one for them.

Bloods and Spinal Fluid Samples
A sample of your child's blood (via venepuncture) and cerebrospinal fluid or CSF (via lumbar puncture) will be taken for the purpose of the study and biobanked. Your child will NOT undergo any *additional* procedures to obtain these samples, we will only ask for extra samples to be taken during routine hospital venepuncture/lumbar puncture. We would like you to know that:

- Blood and spinal fluid samples are taken in all cases of TM as part of routine hospital investigations.
- Your child's study samples will be stored in a registered Human Tissue Act licensed biobank (a secure place for future use). Further studies will ensure a high standard of research review by the study team.
- One such study may be for future DNA analysis. DNA (deoxyribonucleic acid), is found in all cells of the body, and contains the genetic information for the development and working of human beings. Analysing blood samples will allow future research to find out the relationship between our environment (exposures) and our personal susceptibility (genes). We may also come up with better diagnostic tests. If in the future we do find something interesting in analysis of the DNA, we will ask for an extra blood sample to check our findings. We will also try to repeat our findings in a clinical laboratory that undertakes genetic tests, if you would like and if this is possible. Sometimes, our findings might need more tests in the laboratory to know if they are relevant or not. Any results are research findings and are not a clinical test.

Randomisation and Treatment
Once we have collected all the above baseline information (pre-treatment information), your child will be randomised to one of two treatment arms/groups. Randomisation ensures that both groups are the same to start with, so that the different treatments can be compared fairly. Your child has a 50% chance of going into either treatment arm.

Treatment arm 1 will receive the standard hospital treatment for demyelination, intravenous methylprednisolone (IV-MP), for a period of 5 days.

Treatment arm 2 will receive standard therapy with IV-MP for 5 days *plus* treatment with intravenous immunoglobulin (IVIg) for up to 5 days.

Unlike some studies, the doctors will not be 'blinded', meaning that they will know which treatment your child is receiving, and you will also be allowed to know.

Follow Up

Once treatment is complete and you have left hospital, we would like to monitor your child's progress. We will do this during your routine follow-ups in clinic, at 3 months, 6 months and 12 months, and it will take the form of study assessments and questionnaires. These assessments will chart your child's physical recovery, but clinical questionnaires will also give us information on factors such as their progress, quality of life and wellbeing. At the 6 month visit, if routine blood samples are being requested, we will take another biobank sample. Each visit will take about 1 hour. The visits will be conducted by staff who will not know which treatment your child received (this is so they can be unbiased about the results of the assessments) – we will ask you not to tell the assessor which treatment arm your child was on. At the last visit, we will ask whether we can contact you in the future to take part in other studies.

What are the possible disadvantages and risks of taking part?

We foresee no additional risks by taking part in the study, as all medications are already used in general practice, there are no placebos, and as a minimum, every child will receive standard care given in hospitals for their illness.

If your child should receive IVIg treatment, there are some common side effects, but these are transient and can occur in any patient taking IVIg, for any condition. These can include: chills, headache, fever, palpitations, nausea and vomiting, allergic reactions, infusion related reaction, low blood pressure and mild back pain or joint pain. The doctor will talk to you further about these if you require.

During treatment on either arm of the trial, if your doctor does not think that there has been enough improvement in your child's condition, additional treatment with plasma exchange (PLEX) may be considered as a 'rescue therapy'. PLEX involves replacing the plasma in a person's blood. The possible use of a rescue therapy has been built into study procedure, and means that if it is required, it will not affect your child's study status.

What are the possible benefits of taking part?

We cannot promise that participation in this study will provide extra benefits. We do hope, however, that the information provided will help further improve treatment for young people with TM in the future.

PART 2

What if there is a problem whilst we are on the study?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact: <NAME>, Principal Investigator, at (insert email): XXXXX or by calling (insert telephone no) XXXXX.

If you have a complaint, you should talk to your research doctor who will do their best to answer your questions. If you remain unhappy, you can make a formal complaint through the NHS complaints procedure. Details can be obtained through the Guy's and St Thomas' Patient Advisory Liaison Service (PALS) on 0207 1887188, address: PALS, KIC, Ground floor, north wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH . This

study is insured by Guy's & St Thomas' NHS Foundation Trust under the Clinical Negligence Scheme for trials.

All professional staff involved in the study hold professional indemnity to work within Guy's and St Thomas' NHS Trust. In the event that you are harmed during the research and this is due to negligence then you may have grounds for legal action for compensation against Guy's and St Thomas NHS Trust but you may have to pay your legal costs. The normal NHS complaints mechanisms are still available to you.

Will my child's taking part in the research project be kept confidential?

Yes. All the information about your child's participation in this study will be kept confidential in accordance with the Data Protection Act 1998. The information from each patient will be stored in a confidential database, where it will be identified only by a unique PIN number.

Involvement of the General Practitioner/Family doctor (GP)

The family GP will be notified of your child's participation in the trial, and will receive a copy of the assent/consent form.

Will any genetic tests be done?

No specific genetic tests will be carried out.

What will happen to the results of the research study?

It is intended that the results will be published in a reputable medical journal. Your child will not be identified in any report/publication. The results of the study will also be presented in National and International meetings. If you would like a summary of the final results, this will also be made available.

Who is organising and funding the research?

The research is being funded by the National Institute for Health Research (NIHR.ac.uk) and is organised by a research team from the King's Clinical Trials Unit and the Evelina Children's Hospital in London, as part of the King's Health Partners Academic Health Science Centre.

Who has reviewed the study?

The study also has ethical approval from The South-Central Berkshire B Research Ethics Committee and approval from your local hospital's Research & Development Department.

If you have any questions about this study, then please contact the study team members at: <INSERT LOCAL PHONE NUMBER>

Alternatively, if you would like to discuss your participation in the study with someone outside of the study team, you may wish to approach the local Patient Advisory Liaison Service (PALS) on <*INSERT LOCAL PALS NUMBER*>.

Thank you for taking the time to read this information sheet

Centre Number: _____

Patient Identification Number for this trial: _____

ASSENT FORM FOR CHILDREN

(To be completed by the Child/Young Adult 8-16)

Name of Patient: _____

Child /Young Person to circle all they agree with:

Have you read (or had read to you) all of the information about this study?	Yes/No
Has somebody else explained this study to you?	Yes/No
Do you understand what this study is about?	Yes/No
Have you asked all the questions you want?	Yes/No
Have you had your questions answered in a way that you understand?	Yes/No
Do you understand it is OK to stop taking part at any time?	Yes/No
Is it alright to have some extra blood and spinal fluid samples taken?	Yes/No
Are you happy to take part in this study?	Yes/No
Are you happy to take part in future research?	Yes/No
Are you happy for us to use your MRI scan?	Yes/No

If any of your answers are 'no', you can discuss them now – but if you do not want to take part, do not sign your name!

If you do want to take part, you can write your name below

Your name: _____

Date: _____

The doctor who explained this clinical trial to you needs to sign too:

Print Name: _____

Sign: _____

Date: _____

Thank you for taking part.

Clinical trial number: _____

Centre Number: _____

Patient Study Number: _____

CONSENT FORM
(For Parents/Guardians)

Name of Patient**:** _____

	Please initial box
1. I confirm that I have read and understand the information sheet dated **22.10.2014 (version 1.4)** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my child's participation is voluntary and that I am free to withdraw my child from the study at any time without giving any reason, without their medical care or legal rights being affected.	
3. I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my child taking part in this research. I give permission for these individuals to have access to my child's records.	
4. I agree to routine blood and spinal fluid samples during my child's illness(es) and that the results of their MRI can be used for this study.	
5. I agree to blood and spinal fluid samples being taken during my child's illness(es), to be stored on behalf of the research team, by a licensed biobank for the possibility of future studies to be conducted.	
6. I agree to a DNA sample being taken during routine venepuncture and being stored on behalf of the research team, by a licensed biobank for the possibility of future studies to be conducted.	
7. I agree to my child's GP being informed of their participation in the study.	
8. I agree that I can be contacted in the future regarding future studies.	
9. I agree for the study team in London to keep details of my child's name and date of birth for future contact.	
10. **I understand that information held by the NHS and records maintained by The NHS Information Centre and the NHS Central Register may be used to help contact me and provide information about my child's health status.**	
11. I agree for my child to take part in the above study.	

_____	_____	_____
Name of Parent/ Guardian	*Date*	*Signature*
_____	_____	_____
Name of Person Taking Consent	*Date*	*Signature*

Patient Study Number: _____

Clinical trial number: _____

Centre Number: _____

Patient Study Number: _____

CONSENT FORM

Name of Patient**:** _____

Please initial box

1. I confirm that I have read and understand the information sheet dated **22.10.2014 (version 1.4)** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving any reason, without my medical care or legal rights being affected.	
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4. I agree to routine blood and spinal fluid samples during my illness(es) and that the results of my MRI can be used for this study.	
5. I agree to blood and spinal fluid samples being taken during my illness(es) to be stored on behalf of the research team, by a licensed biobank for the possibility of future studies to be conducted.	
6. I agree to a DNA sample to be taken during routine venepuncture and to be stored on behalf of the research team, by a licensed biobank for the possibility of future studies to be conducted.	
7. I agree to my GP being informed of my participation in the study.	
8. I agree that I can be contacted in the future regarding future studies.	
9. I agree for the study team in London to keep my details for future contact.	
10. I understand that information held by the NHS and records maintained by The NHS Information Centre and the NHS Central Register may be used to help contact me and provide information about my health status.	
11. I agree to take part in the above study.	

_____	_____	_____
Name of Patient (over 16)	*Date*	*Signature*

_____	_____	_____
Name of Person Taking Consent	*Date*	*Signature*

Patient Study Number: _____

Biological Samples Collection and Shipment to BioBank

Standard Operating Procedure

Contents

PURPOSE

The purpose of this protocol is to describe procedures for collecting and transporting specimens from STRIVE Trial participants to the appropriate BioBank (contact details page 5).

Wales Neuroscience Research Tissue Bank will receive samples from STRIVE trial centres in Birmingham, Bristol, Liverpool, Manchester and Wales.

The KCL Infectious Diseases BioBank will receive samples from the rest of the STRIVE trial centres.

The samples will be obtained from paediatric and adult patient populations presenting with symptoms of transverse myelitis.

SCOPE

This protocol is written for research personnel at NHS sites participating in STRIVE Trial.

RESPONSIBILITIES

Practitioners taking blood and CSF samples should be GCP trained and their involvement should be clearly recorded on the delegation log. They should have sufficient experience and training to perform these activities safely and at minimum patient discomfort according to local research governance procedures.

SAMPLES REQUIRED

Samples listed in the table below should be collected on the same day if possible. Morning collection will be required in order to allow sufficient time for delivery to the appropriate BioBank.

Tissue to collect	Volume*	Collection Tube	Collected at Baseline (T0)	Collected at 6 months follow up (T3)
Serum	10 ml	SST, allow to sit at least 30 min at room temp.	✓	✓
Plasma	10 ml	EDTA, gently invert to mix 8-10 times	✓	✓
DNA	10 ml	EDTA, gently invert to mix 8-10 times	✓	
PBMC**	10 ml	EDTA or sodium heparin, gently invert to mix 8-10 times	✓	
RNA	10 ml	PAX tube	✓	
CSF	12 ml	Sterile polypropylene tube with lid	✓	

NOTE**: These volumes may not be appropriate for **paediatric patients** but aim to collect as much as possible. ***Minimum volumes for each paediatric sample should be around ***50% of the adult volumes***.

****NOTE**: PBMC samples to be collected from patients who have never been treated with steroids, immune-modulatory or immune-suppressive medication. If there is prior history of treatment with any of the drugs in these categories PBMC samples can be collected if sufficient time has lapsed since the treatment:

- IV pulse steroids: 30 days
- systemic oral steroids: 30 days

- immunomodulatory agent (glatiramer acetate or interferon b): 3 months
- immunosuppressive agent (azathioprine/ methotrexate): 6 months
- biologic therapy: do not collect blood for PBMC

METHOD FOR BLOOD EXTRACTION

1. Prior to blood extraction ensure informed consent from patient and/or guardian according to STRIVE study protocol was obtained.

2. Explain the procedure to participant giving time for any questions and ensure the patient is comfortable with the procedure.

3. Ensure all equipment is ready to hand in a tray next to the participant. Blood sampling tray should contain:

- SST, EDTA, Sodium heparin and PAX collection tubes
- Syringe with a green/blue needle or Vacutainer system with butterfly needle attachment
- Cotton Swab/Gauze
- Alcohol Swab
- Tourniquet
- Plastic gloves

4. Follow local procedures for safe blood extraction and ensure that collection tubes are full.

5. Label the tubes with: patient's **STRIVE PIN number, date and time blood sample was taken.**

6. Complete **STRIVE sample collection form** (see Appendix) which will be couriered to the BioBank with the samples at ambient temperature.

7. **Send to the BioBank as soon as possible to be delivered before 2 pm.**

METHOD FOR CSF EXTRACTION

1. Prior to CSF extraction ensure informed consent from patient and/or guardian according to STRIVE study protocol was obtained.
2. Explain the procedure to participant giving time for any questions and ensure the patient is comfortable with the procedure.
3. Ensure that lumbar puncture tray is complete and ready for use. Usually it will contain:
   - Povidone-iodine (10%) (Betadine®) and/or isopropyl alcohol (70%) with applicators or sterile pads
   - Fenestrated drape
   - Local anesthetic (lidocaine 1%, (10mg/mL) 1-2 mL)
   - Syringe with small needle (1-2 inch, ~23g) for use with local anaesthetic
   - 3.5 inch lumbar puncture needle (22 gauge atraumatic recommended)
   - Sterile polypropylene tubes with caps for CSF collection
4. Position patient appropriately for procedure and follow locally approved standards for safe extraction of CSF. It is recommended that location for extraction is between L3/L4 or L4/L5.
5. Label the tubes with: patient's **STRIVE PIN number, date and time blood sample was taken.**
6. Complete **STRIVE sample collection form** (see Appendix) which will be couriered to the BioBank with the samples.

7. **Send to the BioBank as soon as possible to be delivered before 2 pm.**

In some instances it may not be possible to collect blood and CSF samples on the same day so collect them on two consecutive mornings and deliver each sample to the BioBank as soon as possible on the day of collection.

BIOBOTTLE AND SHIPPING INSTRUCTIONS

1. Place *clearly labelled* blood and CSF tubes (patient study number, date and time of sample collection) inside a plastic bag first, then into the Biobottle. Aim to send all samples from a patient to the BioBank together.
2. Ensure the absorbent material is in the Biobottle.
3. Ensure the correct sample collection forms are placed with the matched blood and CSF samples.
4. Please ensure that all contents are inside the package before closing.
5. Please ensure the outside of the shipment box is clearly labelled with sender's details (the name and address of the person responsible at site for sending the samples with a contact telephone number) as well as the address of the BioBank to which the samples need to be couriered.
6. After taking a sample, the research nurse (or designated site person) at the STRIVE trial centre will call the specialist medical couriers (CitySprint Couriers Tel: 0845 020 3000) to arrange collection and delivery to the appropriate BioBank.
7. Upon booking the courier, a reference number will be provided by CitySprint.
8. **For deliveries to the KCL Infectious Diseases BioBank** the reference number will be communicated via email (biobank@kcl.ac.uk) by the site's designated person.

   The courier will transport the sample to the Secretaries Office, Programme in Infection and Immunity, KCL, 2nd Floor Borough Wing, Guy's Hospital where the receiving individual will confirm receipt of the sample. The Secretaries' Office will ensure rapid sample transfer to BioBank staff who will then email the sender of the sample to confirm receipt of the sample.
9. **For deliveries to the Wales Neuroscience Research Tissue Bank** the reference number will be communicated via email (WNRTB@Cardiff.ac.uk) by the site's designated person. Additionally they can be phoned using telephone number 02920 743454.
10. In addition to the tracking number please quote **'STRIVE Trial'** when alerting the BioBanks that the samples have been collected from the site.
11. If the courier has not collected the samples within 90 minutes, the person who booked the courier should contact CitySprint to find out the status, quoting the reference number, and notify the appropriate BioBank of any delays.
12. If the BioBank staff have not confirmed receipt of the samples within two hours of collection from the trial centre by CitySprint, the courier will be contacted and the sample traced.

TIMING OF SAMPLE DELIVERY

After collection samples should be sent to the BioBank as soon as possible using CitySprint Couriers. Please ensure that the samples are ***not sent*** to the BioBank ***after 2 pm***, Monday to Friday.

Once samples are safely secured inside the Biobox and ready for transfer to BioBank, please phone or email the contacts at the BioBank of their impending arrival so arrangements can be made to store the samples.

NOTE: For samples collected at **6 months follow up**, please contact the relevant BioBank well ahead of time and give them the date when the samples will be sent to them for processing.

PERSONNEL

Members of clinical staff trained to take blood and/or CSF, including doctors and nurses on the unit.

HEALTH AND SAFETY

1. Standard precautions are required. Always wear gloves when handling blood samples.

2. Refer to the risk assessment, hazard data sheets and the Departmental policy at your site for additional safety information.

3. Please take all reasonable efforts to notify the BioBank of any extraneous agents, or biologically active contaminants that the sender is aware of (for example, but not limited to, HIV, hepatitis B, tuberculosis and transmissible spongiform encephalopathies) which may have been or are present in the samples.

BIOBANKS' CONTACT DETAILS

Sample Delivery Address	Lab Co-ordinator	Telephone	Email	Trial Sites
The KCL Infectious Diseases BioBank Secretaries Office Programme of Infection and Immunity Second Floor Borough Wing Guy's Hospital Great Maze Pond London SE1 9RT	Christine Mant John Cason	020 7188 3069 020 7188 1180	Biobank@kcl.ac.uk john.cason@kcl.ac.uk	London Liverpool Oxford Southampton Newcastle Nottingham
Wales Neuroscience Research Tissue Bank For the attention of Dr Sam Loveless Welsh Neuroscience Research Tissue Bank, C/O Reception Desk Henry Wellcome Building Cardiff University Heath Park Campus Cardiff CF14 4XN	Samantha Loveless	029 2074 3454	LovelessS1@cardiff.ac.uk	Birmingham Bristol Manchester Wales

APPENDIX: STRIVE TRIAL SAMPLE COLLECTION FORM

Please ensure that this form is sent to the BioBank with patient's samples but a copy should also be filed with patient's study notes.

Please send the samples to the BioBank as soon as possible after collection.

STRIVE TRIAL SAMPLE COLLECTION FORM

Name of the hospital.....

STRIVE Patient ID:.....

DOB:.....

Gender: Male ☐ Female ☐

Initials:.....

Date sample collected:.....

Time sample collected:.....

Patient did/did not *(please delete as appropriate)* receive steroid/immunomodulatory/suppressive treatments in the last 30 days/ 3 months/6 months.

Total Samples Collected:

TUBE	Quantity (ml)	Study time point	
		T0 (baseline)	T3 (6 M follow-up)
SST			
EDTA			
Sodium Heparin			
PAX tube			
Sterile polypropylene tube with lid			

1. PROTOCOL

1.1 Protocol Short Title/Acronym

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**

1.3 Sponsor

Name:	Guy's and St Thomas' NHS foundation Trust
Contact Person	Jackie Pullen
Address:	Guy's & St Thomas' NHS Foundation Trust 16th Floor, Guy's Tower, Guy's Hospital, Great Maze Pond, London SE1 9RT
Telephone:	020 7188 5732
Fax:	020 7188 8330
Email:	Jackie.Pullen@kcl.ac.uk

1.4 Chief Investigator

Name:	Dr Ming Lim (Consultant Paediatric Neurologist)
Address:	Children's Neurosciences, 1st Floor, D Block South Wing, St Thomas' Hospital, SE1 7EH
Telephone:	020 7188 4002
Fax:	020 7188 4269
Email:	Ming.Lim@gstt.nhs.uk

1.5 Name and address of Co-Investigator(s), Statistician, Laboratories etc

Name:	Dr Michael Absoud (Consultant and Research Fellow, Paediatric Neurodisability)
Position/ Role:	Co-Investigator, project co-ordinator and manager (Paediatrics)
Address:	Children's Neurosciences, 1st Floor, D Block South Wing, St Thomas' Hospital, SE1 7EH
Telephone:	020 7188 3995
Fax:	020 7188 4665
Email:	michael.absoud@gstt.nhs.uk

Name:	Dr Anu Jacob (Consultant Neurologist)
Position/ Role:	Co-investigator, project co-ordinator and manager (Adults)
Address:	The Walton Centre NHS Foundation Trust, Lower Lane, Fazakerley, Liverpool, L9 7LJ
Telephone:	0151 529 5420
Fax:	0151 529 5513
Email:	anu.jacob@thewaltoncentre.nhs.uk

Name:	Prof Gavin Giovannoni (Professor of Neurology)
Position/ Role:	Co-investigator, methodological input and clinical trial expertise
Address:	Centre for Neurosciences, Barts and The London School of Medicine and Dentistry, 4 Newark Street, London, E1 2AT
Email	g.giovannoni@qmul.ac.uk

Name:	Dr Jackie Palace (Consultant Neurologist)
Position/ Role:	Co-investigator, methodological input, clinical input and clinical trial expertise
Address:	Dept of Neurology, Neurosciences Offices, Level 3, West Wing, John Radcliffe Hospital, Oxford, OX3 9DU
Email:	jacqueline.palace@ndcn.ox.ac.uk

Name:	Prof Neil Robertson (Prof of Neurology)
Position/ Role:	Co-Investigator and Coordinator: Central Biobank
Address:	Institute of Psychological Medicine and Clinical Neurosciences, 2nd Floor, B-C Link Corridor, Cardiff University School of Medicine, UHW Main Building, Heath Park, Cardiff CF14 4XN
Telephone:	029 20 745 403, ext. 5403
Email:	RobertsonNP@cardiff.ac.uk

Name:	Dr Mike Pike (Consultant Paediatric Neurologist)
Position/ Role:	Co-Investigator and methodological input
Address:	John Radcliffe Hospital, Oxford
Email:	Mike.Pike@ouh.nhs.uk

Name:	Prof Paul McCrone (Professor of Health Economics)
Position/ Role:	Co-Investigator, Health economic analysis
Address:	Centre for the Economics of Mental and Physical Health, P024 Institute of Psychiatry, King's College London, Denmark Hill, London, SE5 8AF
Email:	paul.mccrone@kcl.ac.uk

Name:	Dr Peter Brex (Consultant Neurologist)
Position/ Role:	Co-Investigator, methodological input and clinical expertise
Address:	Department of Neurology, 9th floor, Ruskin Wing, Denmark Hill, King's College Hospital, London, SE5 9RS
Email	p.brex@nhs.net

Name:	Dr Olga Cirrarelli (Reader in Neurology)
Position/ Role:	Co-Investigator, methodological input and clinical expertise
Address:	UCL Institute of Neurology, Queen Square, London WC1N 3BG
Telephone:	020 3448 3419
Fax:	020 7813 6505
Email:	olga.cirrarelli@uclh.nhs.uk

Name:	Prof Andrew Pickles (Prof of Biostatistics)
Position/ Role:	Statistician & methodological input
Address:	Institute of Psychiatry, Box PO20, De Crespigny Park, London, SE5 8AF
Email:	andrew.pickles@kcl.ac.uk

Name:	Dr Jennifer Hellier (Statistician)
Position/ Role:	Primary Statistician & methodological input
Address:	Department of Biostatistics, Institute of Psychiatry, Box PO20, De Crespigny Park, London, SE5 8AF
Telephone:	0207 848 0323
Email:	jennifer.hellier@kcl.ac.uk

Name:	Ms Caroline Murphy
Position/ Role:	Co-Investigator/ Operational Director, KCTU
Address:	King's Clinical Trials Unit, King's College London, PO64, M2.06, Institute of Psychiatry, London, SE5 8AF
Telephone:	0207 848 5273
Fax:	0207 848 5229
Email:	caroline.murphy@kcl.ac.uk

Name:	Ms Joanna Kelly
Position/ Role:	Co-investigator/ Data Management Strategic Lead
Address:	King's Clinical Trials Unit, King's College London, PO64, M2.06, Institute of Psychiatry, London, SE5 8AF
Telephone:	0207 848 5273
Fax:	0207 848 5229
Email:	joanna.kelly@kcl.ac.uk

Name:	Mrs Rosemary Howe
Position/ Role:	Clinical Trial Manager
Address:	9th Floor, Capital House, Guy's Campus, 42 Weston Street, London SE1 3QD

Telephone:	020 7848 6245
Fax:	TBC
Email:	TBC

Name:	Dr Andrea Wartenberg
Position/ Role:	Vice President Corporate Clinical Research
Address:	Biotest AG Landsteinerstraße 5 D-63303 Dreieich Germany
Fax:	0049 6103/801-341
Telephone:	0049 6103/801-497

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 NHS Foundation Trust - Barts Health NHS Trust
Liverpool	05	06	- Alder Hey Children's NHS Foundation Trust - 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 NHS Trust, Wales
Bristol	13	14	- North Bristol NHS Trust - University Hospital Bristol NHS Trust
Manchester	15	16	-Central Manchester University Hospitals NHS Foundation Trust - Royal Salford NHS Foundation Trust
Southampton	17	18	University Southampton NHS Trust
Newcastle	19	20	Newcastle Hospitals NHS Foundation Trust
Nottingham	21	22	Nottingham University Hospitals NHS Trust
Edinburgh		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:	Guys 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) ▪ Lack 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 (Wingerchuck 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 divided doses over 5 days (or given over 2 days 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:	draft v2.3 09/01/2015
Version And Date Of Protocol Amendments:	V2.0 30/09/2014 V2.1 15/10/2014

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	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, 2014). 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, 2012), 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 1988). 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 a 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 ≥13at 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 (variations of 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 divided doses over 5 days
- 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 divided doses over 2 days

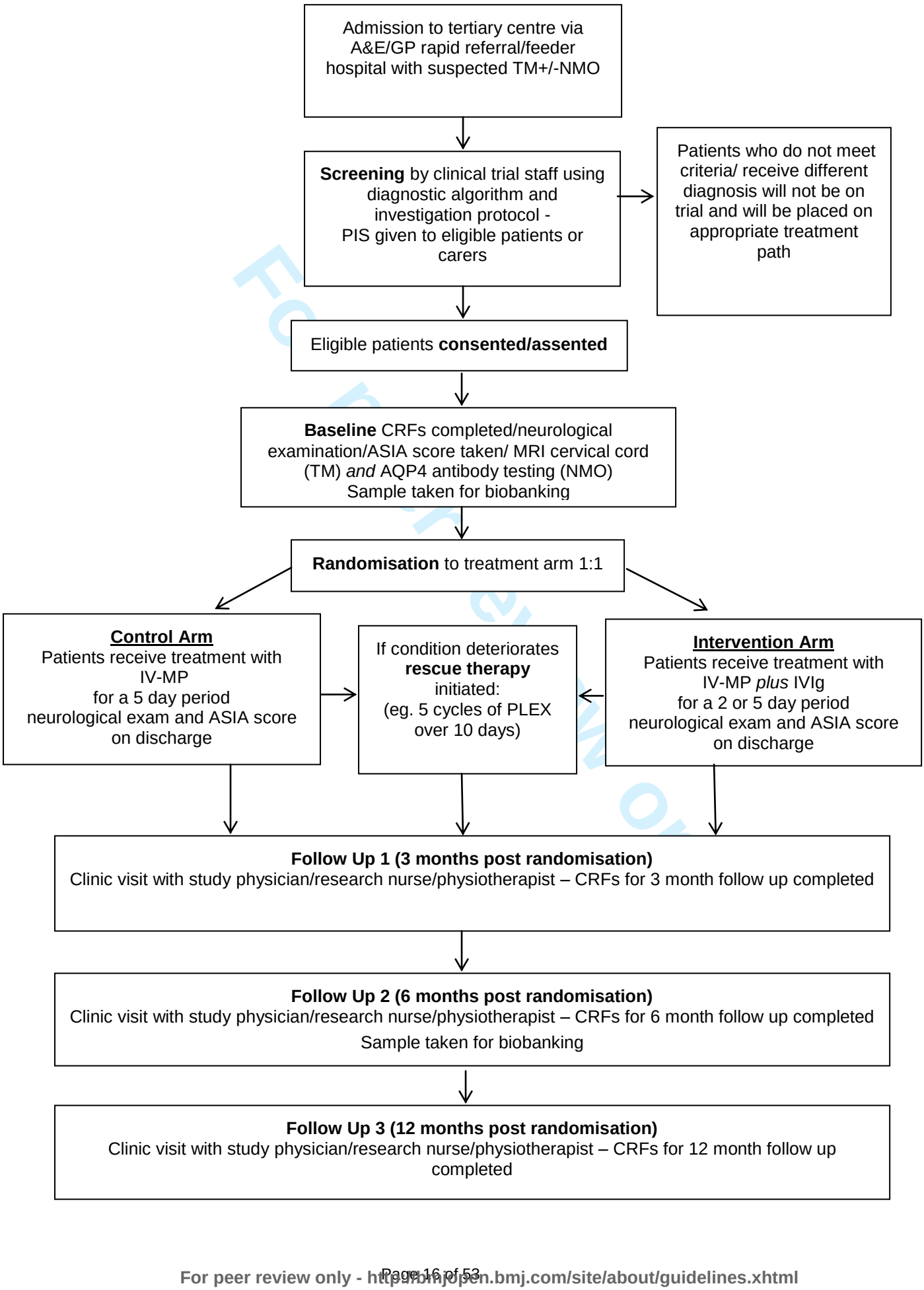
Patients may be recruited and randomised up to 5 days from the date of first commencing steroid therapy or up to 21 days from the onset of symptoms (if definitely known)..

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 secured 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 coordinator. 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 practice 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 with PLEX will be instituted, in accordance with local guidelines (please see section 6.5 above). 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 (Wingerchuck 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 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

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 11 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 Patient Registration

After consent has been signed, the patient will be registered on the MACRO system, which can be accessed online by a trained member of trial staff who has been allocated a username and password (via trial manager). The system is accessed at **www.ctu.co.uk** by clicking **'MACRO EDC v4'** in the **Useful Links** box on the lower right hand side of the page. Following entry of registration details the system will generate a unique patient identification number (PIN) which will be used, with patient initials, for that patient throughout the study on all CRFs and eCRFs, and will be the only method of identification (for information on the MACRO system (see section 20). The PIN will be a five digit number, the initial two digits corresponding to the centre the patient was recruited from.

8.5 Randomisation Procedure

Patients will be randomised to treatment arms via an online system based at King's Clinical Trials Unit (KCTU). The system can be accessed at **www.ctu.co.uk** by clicking **'randomisation – advanced'**. This system can only be accessed by trained trial staff that have previously been allocated a username and

password. Requests for passwords are via the Trial Manager to the King's CTU. Details of individuals responsible for patient randomisation will be kept on local delegation of duties log.

Please make sure that baseline data has been collected for the patient just prior to randomisation (see section 9 for further details).

Also note that randomisation system is *not* linked to the MACRO (main study) database (see section 20).

Allocation to trial arms will be at the level of the individual patient, using stratified block randomisation. The block will randomly vary in length of 2 and 4, and patients will be stratified by service type (adult or child). The randomisation system will automatically generate emails at the point of randomisation which will be sent to appropriate members of the study team. The trial manager and those administering treatment are unblinded and will be informed of the allocated treatment arm. Those who will carry out follow up assessments will be blinded, therefore they will just receive notification of randomisation in order to start scheduling appointments. A study specific prescription will be completed and sent to pharmacy for dispensing. Any problems with the online randomisation system should be reported to the trial manager or to the King's CTU at CTU@kcl.ac.uk / 0207 848 0532.

8.6 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 (ie. 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.

8.7 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

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 with following data items:

Date of Admission, Patient ID (NHS or Hospital number), Patient DOB, Suspect TM (yes/no), Eligible for the study (yes/no), Consented to take part (yes/no), Reason for not being included in the study, Date randomised, Study ID, Date 3 months follow up, Date 6 months follow up, Date 12 months follow up, Any comments. An excel spreadsheet template for a screening log will be sent to each trial centre by the Trial Manager.

If patients/ guardians consent to take part in the study please ensure that randomisation takes place as soon as possible but IVIg treatment has to be immediately available for patients randomised to treatment group.

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, we envisage that a proportion of patients will receive IVIg with IV MP on at least one day as shown in this table:

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	TD2	TD 3	TD 4	TD 5
IV MP (Control arm)	◄- - - - - - - - - - - - - - X - - - - - - - - - - - - - - ► (A total of 5 days treatment, which can commence on day of admission. Patients may be recruited up to 5 days from the date of commencing IV MP (D1))								
IV MP (Intervention arm)	◄- - - - - - - - - - - - - - X - - - - - - - - - - - - - - ► (A total of 5 days treatment, which can commence on day of admission. 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**			

If patient's symptoms worsen during treatment or there is no improvement at the end of treatment the patient will have prolonged hospitalisation and rescue therapy should be applied (as shown in table below):

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.

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 also to **Appendix 3** for additional details of study procedures.

ASIA IMPAIRMENT SCORE (AIS) is the main eligibility criterion as well as the primary outcome. It should be obtained immediately before randomisation as baseline measure, even if it was recorded during screening or any earlier time point prior to randomisation.

If the patient deteriorates and needs to have rescue therapy please evaluate ASIA motor, sensory and impairment scores before the rescue therapy is initiated.

Each assessor needs to have training and obtain certification for ASIA Sensory and Motor Scoring evaluation (see: http://lms3.learnshare.com/home.aspx). Please forward copies of the certificates to the STRIVE Trial Manager.

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.

Schedule Table:

Schedule Treatment day (D) Timepoint (T)	**T0** (Screening, baseline and prediagnosis tests)	**T1** (Treatment and discharge)							**T2** 3M	**T3** 6M	**T4** 12M	Withdrawal
		TD 1‡	TD 2	TD 3	TD 4	TD 5	*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	x								x	S	x	
≥13 yrs EQ-5D-5L	x								x	S	x	
≥13 yrs SCI QoL Basic dataset									x	S	x	
CSRI									x	S	x	
≥13 yrs SCI Bladder										T	x	
≥13 yrs SCI Bowel										T	x	
5-7yrs Peds QL										T	x	

2-4 yrs Peds QL										**T**	**x**	
Treatment form						**x**						
Concomitant medications								**x**	**x**	**x**	**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**	**x**	**x**	**x**	**x**						
Study Status Form									**x**	**x**	**x**	
*Withdrawal form (at any time point)												**x**

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

‡ IVIg Treatment Day1 (TD1) = shown in this table separately but the first day of IVIg treatment should happen on the same day as day of randomisation

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

9.2 By Visit

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

Screening and baseline assessments will be made in the tertiary centres by a study physician/research nurse, and as treatment has not yet been allocated, blinding will not be of issue.

Post randomisation, all assessments and study data taken during the hospital stay, and all follow up assessments 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.

9.3 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. 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 (http://content.learnshare.com/courses/120/440012/story.html).

During the trial, the Kurtzke Neurological exam (Neurostatus score) and the SCI scales for Bladder, Bowel and Pain will also be used. Any members of study team who do not routinely use these exams/scales will also need to undergo training from the PI. All training must be recorded in the Staff Training Log in the site Master Files.

9.4 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. 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 SOP will be provided to all investigators.

9.5 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 on MRI sequences, but wherever possible, gadolinium enhancement should be requested. Reports should 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

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

All assessments will be carried out by a physician/research nurse/physiotherapist blinded to treatment and will be reported using the appropriate assessment tools and questionnaires.

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:

Go to www.ctu.co.uk and click the link to MACRO EDC V4 on the lower right hand side of the screen.

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 2 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). Biotest AG will provide the study drugs.

24. Signatures

_____ _____

Chief Investigator Date

Print name

_____ _____

Statistician (if applicable) Date

Print name

25. References

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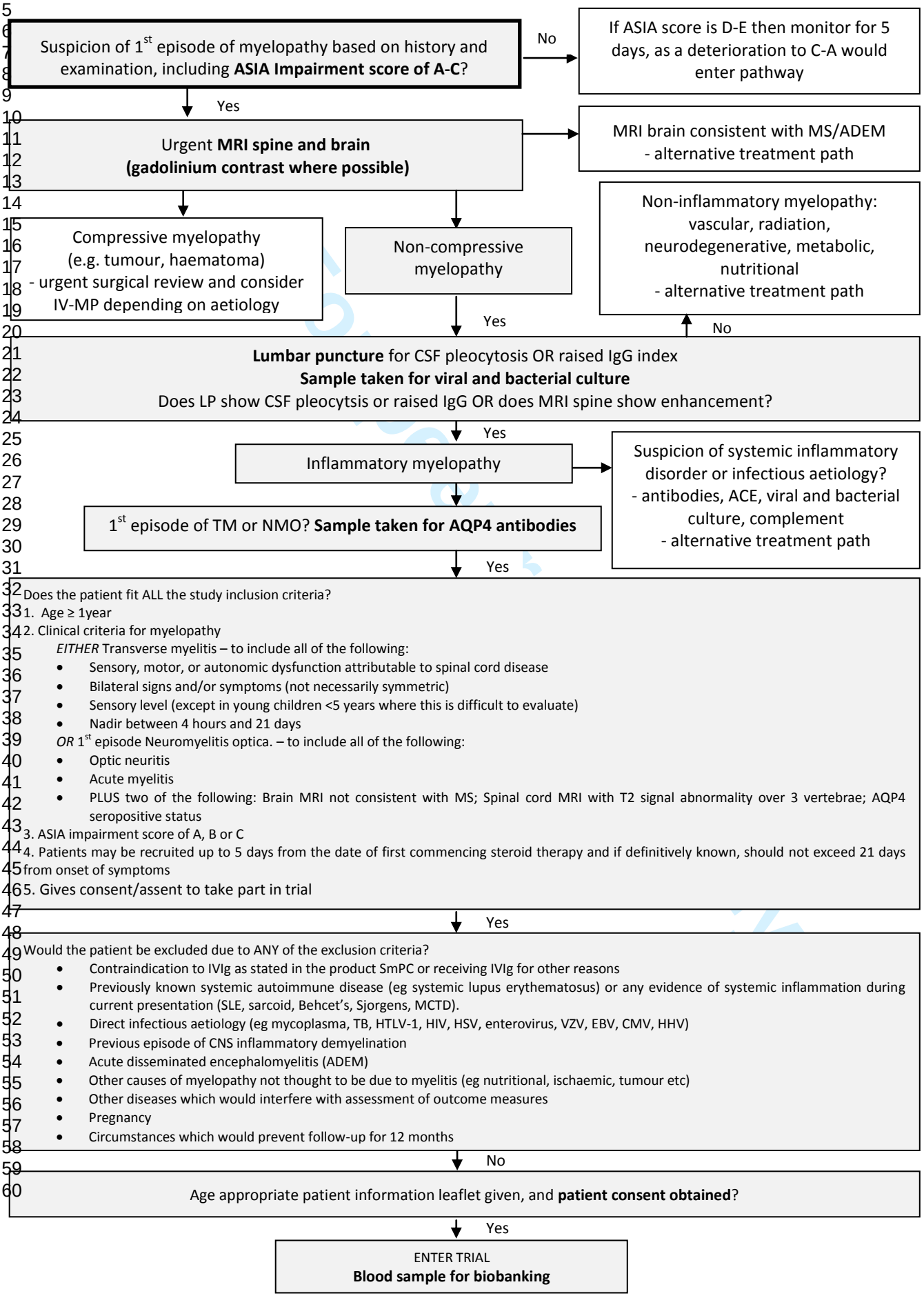
26. Appendices

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

Appendix 2: Clinico-radiological Diagnostic Algorithm



Appendix 3: Trial Procedures by Visit

IMPORTANT: All staff conducting ASIA, SCI and Kurtzke's functional and EDSS assessments MUST undergo training which has to be documented in the Site Training Log.

INITIAL CONTACT

Screening

A screening log will be kept at all sites (see section 9).

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
- ASIA Motor and Sensory (if patient ≥ 5 years of age) Scores including AIS (ASIA Impairment score of A, B or C is necessary for eligibility*)
- 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

* 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 recruited and 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.

Consent

If the patient meets all of the eligibility criteria, the clinician 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 patents 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.

- Equipment/Forms required:
- Patient Information Sheets (PIS) - child/adolescent/adult/parent
- Consent/Assent forms - child/adolescent/adult

After consent, study data can officially be collected:

- ASIA Sensory and Motor scores including AIS
- Results of pre-diagnosis tests form can be submitted as study data (including AQP4 and culture results when available).

Registration and Pre-Treatment (baseline) Assessment

As soon as consent has been obtained the patient should be **registered** on STRIVE trial database. The database is accessible at the following URL. 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. This number together with patient's initials and DOB will be required by STRIVE Randomisation database (see below). 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, 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 Syste,s and EDSS form)
- ASIA Motor, Sensory and Impairment Score fom

- Biobank Sample form

Randomisation = study time point T0

The patient will be randomised via the King's CTU online randomisation service (URL: 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, IV-Ig 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 and the score just prior to randomisation has to be recorded in the database.Forms required for randomisation:

Randomisation form

Following randomisation, all examinations and assessments should be performed by staff blinded to treatment.

Treatment = T1

The total study treatment period will be 5 days (see Section 9.1 for summary table) but if there are delays between admission and randomisation it can be extended up to 9 days overall.

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

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). 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
- Rescue Therapy form

Completion of Treatment/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
- Neurostatus Examination (Kurtzke Neurological and EDSS) form
- Rescue Therapy form (if required)
- Relapse form (if required)
- Withdrawal form (if required)

FOLLOW UP VISITS

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)
- Neurostatus scoring (Kurtzke's functional systems and EDSS)
- EQ-5D-Y (for patients aged 7-12 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 (separate form in the database)

Secondary endpoint:

ASIA Motor and Sensory scales components

Neurostatus exam (Kurtzke's functional systems and EDSS)

EQ-5D-Y (for patients aged 7-12.99 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 endpoint:

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

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 (separate form in the database)

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 7-12.99 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.

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/

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

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

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

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 $\bar{p} = \frac{1}{2}(p_C + p_E)$.

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

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

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.

APPENDIX 6: Professional Advert

Insert local logos

STRIVE

Insert local logos

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

BMJ Open

Protocol for a multicentre randomiSed controlled TRial of IntraVEnous immunoglobulin versus standard therapy for the treatment of transverse myelitis in adults and children (STRIVE)

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008312.R1
Article Type:	Protocol
Date Submitted by the Author:	24-Apr-2015
Complete List of Authors:	Absoud, Michael; Evelina London Children's Hospital at St Thomas' Hospital, Children's Neurosciences Gadian, Jonathan; Evelina London Children's Hospital at St Thomas' Hospital, Children's Neurosciences Hellier, Jennifer; King's College London, Department of Biostatistics, Institute of Psychiatry, Psychology and Neuroscience Brex, Peter; King's Health Partners Academic Health Science Centre, Department of Neurology, King's College Hospital NHS Foundation Trust Ciccarelli, Olga; National Hospital for Neurology and Neurosurgery, Queen Square, UCL Institute of Neurology Giovannoni, Gavin; Blizard Institute, University of London and Bart's Health NHS Trust, Centre for Neuroscience and Trauma Kelly, Joanna; King's College London, King's Clinial Trials Unit McCrone, Paul; King's College London, Centre for the Economics of Mental and Physical Health, Institute of Psychiatry Murphy, Caroline; King's College London, King's Clinial Trials Unit Palace, Jacqueline; John Radcliffe Hospital, Clinical Neurology Pickles, Andrew; King's College London, Department of Biostatistics, Institute of Psychiatry, Psychology and Neuroscience Pike, Michael; Oxford University Hospitals NHS Trust, Department of Paediatric Neurology Robertson, Neil; Cardiff University and Cardiff and Vale NHS Trust, Institute of Psychological Medicine and Clinical Neurosciences Jacob, Anu; The Walton Centre NHS Foundation Trust, The Walton Centre Lim, Ming; Evelina London Children's Hospital at St Thomas' Hospital, Children's Neurosciences
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Medical management, Paediatrics, Immunology (including allergy), Health economics, Research methods
Keywords:	HEALTH ECONOMICS, IMMUNOLOGY, NEUROLOGY, Paediatric neurology < PAEDIATRICS, STATISTICS & RESEARCH METHODS, Clinical trials < THERAPEUTICS

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

Co-Authors: Absoud M*[1], Gadian J*[1], Hellier J[2], Brex PA[3], Cirrarelli O[4], Giovannoni G[5], Kelly J[6], McCrone P[7], Murphy C[6], Palace J[8], Pickles A[2], Pike M[9], Robertson N[10], Jacob A[11], Lim M[1].

* Joint first authors

Corresponding Author: Dr Ming Lim

Address of Corresponding Author: Children's Neurosciences, Evelina Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, King's Health Partners Academic Health Science Centre, Westminster Bridge Road, London, SE1 7EH. ming.lim@gstt.nhs.uk
Phone: 0044 2071884002 Fax: 0044 2071884269

Addresses of Co-authors:

1. Children's Neurosciences, Evelina Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, King's Health Partners Academic Health Science Centre, London (ML, MA, JG).
2. Department of Biostatistics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London (JH, AP).
3. Department of Neurology, King's College Hospital NHS Foundation Trust, King's Health Partners Academic Health Science Centre, London (PB).
4. UCL Institute of Neurology, Queen Square, London (OC).
5. Centre for Neuroscience and Trauma, Blizard Institute, University of London and Bart's Health NHS Trust, London (GG).
6. King's Clinical Trials Unit, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London (JK, CM).
7. Centre for the Economics of Mental and Physical Health, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London (PM).
8. Department of Neurology, Oxford University Hospitals NHS Trust, Oxford (JP).

9. Department of Paediatric Neurology, Oxford University Hospitals NHS Trust, Oxford (MP).

10. Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University and Cardiff and Vale NHS Trust, Cardiff (NR).

11. The Walton Centre, Walton Centre NHS Foundation Trust, Liverpool (AJ).

Keywords (max 5): immunoglobulins, intravenous; myelitis, transverse; neuromyelitis optica; randomised controlled trial; clinical trials unit.

Word Count: 3890

Number of Figures: 1

Number of Tables: 1

Number of References: 24

Number of Supplementary Files: 4

ABSTRACT

Introduction

Transverse myelitis (TM) is an immune-mediated disorder of the spinal cord which causes motor and sensory disturbance, and limited recovery in 50% of patients. Standard treatment is steroids, and patients with more severe disease appear to respond to plasma exchange (PLEX). Intravenous immunoglobulin (IVIG) has also been used as an adjunct to steroids, but evidence is lacking. We propose the first randomised control trial in adults and children, to determine the benefit of additional treatment with IVIG.

Methods and analysis

170 adults and children aged over 1 year with acute first episode TM or neuromyelitis optica (with myelitis) will be recruited over a 2.5 year period and followed-up for 12 months. Participants randomised to the control arm will receive standard therapy of intravenous methylprednisolone (IVMP). The intervention arm will receive the above standard therapy, plus additional IVIG (total dose 2g/kg).

Primary outcome will be a 2 point improvement on the American Spinal Injury Association (ASIA) Impairment scale at 6 months post-randomisation by blinded assessors. Additional secondary and tertiary outcome measures will be collected: ASIA motor and sensory scales, Kurtzke expanded disability status scale, International Spinal Cord Injury (SCI) Bladder/Bowel Data Set, Client Services Receipt Index, Pediatric Quality of Life Inventory, EQ-5D, SCI Pain and SCI Quality of Life Data Sets. Biological samples will be biobanked for future studies. Health economics analysis will be performed to calculate cost-effectiveness. After 6 months recruitment there is a planned futility analysis.

Ethics and Dissemination

Research Ethics Committee Approval was obtained: 14/SC/1329. Current protocol: v3.0 (15/01/2015). Study findings will be published in peer reviewed journals.

Registration and Funding

This study is registered with EudraCT (REF: 2014-002335-34); and ISRCTN (REF: 12127581). This project is funded by the National Institute for Health Research, Health Technology Assessment (project number 11/129/148). IVIG will be provided by Biotest AG.

Strengths and limitations of this study

- The first randomised multi-centre UK trial in children and adults with TM/NMO, recruiting 170 patients over 2.5 years with a 12 month follow-up period.
- Outcome measures will include motor, sensory, functional and quality of life measurements by blinded assessors.
- Health economics analysis will include health and social care costs.
- Findings may inform treatment decisions in other rare, inflammatory CNS disorders.
- High recruitment rate required due to low incidence of condition.

INTRODUCTION

Transverse myelitis (TM) is a rare inflammatory disorder of the spinal cord affecting approximately 350 children and adults annually in the UK.[1, 2] Histologically TM is characterised by spinal cord immune cellular infiltration, and pathogenesis is mediated by a variety of immunological mechanisms.[3] Clinical features include a rapid onset of motor, sensory and autonomic dysfunction; and a prolonged recovery phase which may continue for up to four years.[4] Diagnostic criteria for TM, were established by the TM Consortium Working Group in 2002, to distinguish TM from other conditions including MS and clinically isolated syndrome.[5] A proportion of patients initially diagnosed with TM will subsequently relapse, often with involvement of other parts of the central nervous system and may often be diagnosed with either multiple sclerosis (MS) or neuromyelitis-optica (NMO). However, a proportion of patients remain as relapsing transverse myelitis of as yet unknown aetiologies.

NMO is a relapsing subset of TM, caused by antibodies to aquaporin-4, an astrocytic water channel.[6] Clinically, patients have predominantly recurrent episodes of myelitis and optic neuritis. Initial presentation may be with myelitis alone, making it clinically and radiologically indistinguishable from TM, and patients are thus subjected to the same acute therapeutic strategies.

The American Spinal Injury Association (ASIA) international standards for neurological classification of spinal cord injury enables a standardised assessment of neurological outcome, where A is no sensory or motor function in S4-5, and E is normal function.[7] Retrospective data from paediatric cohorts suggest that 30% have ASIA A-C or expanded disability status scale (EDSS) ≥4 after TM,[8] and a retrospective French multicentre study in adults, found that 36% had a poor prognosis as defined by death or non-ambulatory status with current therapy.[9] Since this is primarily a disease of younger people, this results in significant cumulative demands on health and social care resources.

There are no robust controlled trials in children or adults to inform on the optimal treatment of TM. Standard treatment with intravenous methylprednisolone (IVMP) is based on class IV evidence that it shortens relapse duration and speeds recovery in exacerbations of adult multiple sclerosis.[6, 10-12] Given the disease severity and poor outcomes, plasma exchange

(PLEX) has been used in addition to standard therapy. Addition of PLEX showed benefit in two studies: a retrospective analysis of 122 adults with TM;[10] and a small randomised controlled trial (RCT) in adults with steroid unresponsive acute central nervous system (CNS) demyelination which included 4 patients with TM.[13] However, PLEX is not universally available in the NHS, particularly at short notice and on weekends, and can be technically difficult and costly to administer.[14]

Randomised controlled trials have demonstrated IVIG efficacy in a number of neurological conditions.[15] In steroid-unresponsive CNS demyelination IVIG is often used, although supporting data is limited to small case series and single case reports.[16, 17] IVIG appears to inhibit complement binding, neutralise pathogenic cytokines, down-regulate antibody production, enhance remyelination, and modulate phagocytosis and T-cell function.[18] The majority of these factors are common across inflammatory disorders of the CNS including TM,[19] providing a strong rationale for its use. The availability, ease of administration, familiarity and safety also make IVIG an attractive option in the acute setting.

Trial Objectives and Design:

This multi-centre, single blind, parallel group RCT will generate evidence to inform clinical and health economic decisions regarding IVIG use in adults and children with TM.

Primary Objective:

1. To evaluate if additional and early treatment with IVIG is of extra benefit in TM when compared to the current standard therapy of IVMP.

Secondary Objectives:

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. Biobanked 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.

METHODS

Study Setting

Treatment and follow-up will be in the participating tertiary neurology centres, and recruitment will also occur from feeder district general hospitals and rapid GP referrals. For further details on participating centres and trial registration please see Appendix 1.

Eligibility Criteria

Inclusion Criteria

Patients must satisfy all inclusion criteria to be eligible for recruitment. Patients will be eligible if all of the following apply at the time of randomisation:

1. Age 1 year or over
2. Diagnosis of EITHER acute first onset transverse myelitis (using the TM Consortium Working Group 2002 criteria[6]) – patients must fulfil all of the following criteria:
    i. Sensory, motor, or autonomic dysfunction attributable to spinal cord disease
    ii. Bilateral signs and/or symptoms (not necessarily symmetric)
    iii. Sensory level (except in young children <5 years where this is difficult to evaluate)
    iv. Lack of MRI brain criteria consistent with multiple sclerosis[20]
    v. Progression to nadir between 4 h and 21 days

    OR first presentation of neuromyelitis optica (using standardised criteria[21]) – patients must fulfil both absolute criteria:
    i. Optic neuritis
    ii. Acute myelitis

    plus two out of three supportive criteria (as AQP4 is often not available acutely, only the first two supportive criteria would be applied):
    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 IgG seropositive status
3. ASIA Impairment Score of A-C
4. Randomisation to occur no later than day 5 of steroids, and, if definitely known, within 21 days from symptom onset.
5. Give assent (8-16 years)/consent to participate in the trial

Exclusion Criteria

In addition to failing to meet the inclusion criteria, exclusion criteria include any of the following.

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

Interventions

Patients randomised to the **control arm** of this study will be prescribed IVMP. Paediatric patients will receive 30mg/kg or 500mg/m^2 capped to a maximum dose of 1g/day for 5 days. Adult patients will be given 1g/day for 5 days. Clinicians may follow this with an oral steroid taper according to local practice.

Patients randomized to the **intervention arm** will receive the above standard therapy *plus* additional IVIG at a total dose of 2g/kg. Doses will be divided over 2 days (children <41.2kg) or 5 days (all other patients) and individual doses may vary slightly to minimise drug wastage and anticipate for difficult intravenous access in small children.

Treatment failure will be defined as no improvement 14 days after presentation and/or 5 days after completion of treatment, and will be documented. Rescue therapy may be initiated at this point. Given the therapeutic effect of PLEX, treatment will be standardised to comprise 5 cycles in which at least 75% of plasma volume is exchanged, with a gap of 24-48 hours between cycles. An additional course of IVMP may be given if there is a delay between the decision to start PLEX and therapy initiation, at the discretion of the treating clinician. The duration and intensity of neuro-rehabilitation input will be recorded to enable comparison between groups.

Outcome measures

Outcome measures have been selected to give a 'hard' clinical endpoint that will have clinical significance, and will be assessed at the local centre by a blinded assessor. To minimise loss to follow-up, assessments are timed to coincide with routine clinical follow-up. All outcome measures are internationally accepted scales, and the primary outcome measure is the ASIA Impairment scale, which is used to measure disability in TM.[22] A six-month time-point has been selected, as the majority of neurological recovery is likely to have occurred by this point. Additional data-points will be taken at 3 and 12 months to aid statistical analysis.

Primary Outcome Measure

1. A 2 point or greater improvement in the ASIA scale (classified A-E) at 6 months post randomisation when compared to baseline, will indicate a positive outcome

Secondary Outcome Measures

2. A change in ASIA motor scale (0-100) and sensory scale (0-112)
3. A change in Kurtzke expanded disability status scale (EDSS) with Neurostatus scoring
4. EQ-5D-Y (patients aged 8-12 years at presentation) or EQ-5D-5L (patients aged ≥13 years at presentation)
5. International SCI Quality of Life Basic Data Set (patients aged ≥13 years)
6. Client Service Receipt Inventory (CSRI)

Tertiary Outcome Measures

7. International SCI Bladder/Bowel Data Set (patients aged ≥13 years)
8. International SCI Pain Basic Data Set (patients aged ≥13 years)
9. Pediatric Quality of Life Inventory TM™ (PedsQL Parent Report for Toddlers) (patients aged 2-4 years)
10. Pediatric Quality of Life Inventory TM™ (PedsQL Parent Report for Young Children) (patients aged 5-7 years)

<<Figure 1 mono>>

Figure 1: Flow chart showing the process of patient recruitment, treatment and follow-up.

Participant Timeline

Patients will be enrolled to the study for 1 year (Table 1).

Schedule Treatment day (D) Timepoint (T)	**T0** (Screening, baseline and pre-diagnosis tests)	**T1** (Treatment and discharge)							**T2** 3M	**T3** 6M	**T4** 12M	Withdrawal
		TD 1‡	TD 2	TD 3	TD 4	TD 5	*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 – e.g. 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	**X**								**X**	**S**	**X**	
≥13 yrs EQ-5D-5L	**X**								**X**	**S**	**X**	
≥13 yrs SCI QoL Basic dataset									**X**	**S**	**X**	
CSRI									**X**	**S**	**X**	

≥13 yrs SCI Bladder										T	X	
≥13 yrs SCI Bowel										T	X	
5-7yrs Peds QL										T	X	
2-4 yrs Peds QL										T	X	
Treatment form						X						
Concomitant medications								X	X	X	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	X	X	X	X						
Study Status Form									X	X	X	
*Withdrawal form (at any time point)												X

Table 1: Timeline of trial interventions. P–primary outcome measure, S–secondary outcome measure, T–tertiary outcome measure. ‡ Treatment Day 1: IVIG treatment (if applicable) to start on the same day as randomisation. Steroids may be commenced up to 5 days prior to randomisation. *Rescue therapy, relapse and withdrawal forms may only be necessary for a small subset of patients. † Adverse events will be collected throughout the study.

Trial Duration

The project will take 3.5 years. Patient recruitment will take place over the first 30 months, and collection of data will continue until 42 months.

Sample size

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, based on available data from epidemiological studies.[2, 7] The sample

size calculation is based on the conservative assumption of no correlation between repeated measures. Under these assumptions, 76 patients per group will provide 90% power and 5% type II errors for a two-sided test. The sample size will be inflated for attrition, based on our experience and the design which minimises loss to follow up, we estimate 10% attrition. This requires recruitment of 170 patients (85 participants per arm).

The ASIA total motor score (0-100) is a secondary outcome. Stata `*sampsi*` indicates that using Analysis of Covariance 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

Recruitment Plan

TM has an estimated UK incidence of 350/year, and the study centres cover approximately half of the UK population. Assuming a recruitment rate of 39% over a period of 2.5 years we would expect to recruit 170 patients. This recruitment rate is based on a patient and public consultation within the TM society, given that patients will be admitted with a devastating weakness, and the control arm will be receiving standard intervention.

Randomisation

Prior to randomisation but after consent, site staff will register a recruit on the web-based electronic data capture system (InferMed MACRO), hosted at the King's Clinical Trials Unit (KCTU). Each will be assigned a unique study patient identification number (PIN) by the system. Once baseline assessments are complete, the trained trial staff will access KCTU randomisation system and randomise the patient at the individual level using stratified block randomisation by service type (adult or child); the block will randomly vary in size. Treatment allocation will be at a ratio of 1:1. Randomisation will occur during office hours when IVIG is available. Patients eligible for trial recruitment presenting outside of these times will be commenced immediately on IVMP, and will be randomised at the first available opportunity.

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. Staff carrying out study assessments and statistical analyses will be blinded to intervention.

Data collection methods

Kurtzke neurological examination, ASIA Impairment Score, ASIA Motor and Sensory Score and EDSS scores will be completed, together with treatment, discharge and follow-up forms (see Figure 1). All assessments should ideally be performed by the same, blinded assessor, who may be a study physician, physiotherapist or research nurse. All assessors will have successfully completed ASIA and EDSS online training modules (further information detailed in Appendix 1). Biological samples will be collected, processed and stored as detailed in Appendix 3.

Withdrawal

Patients may withdraw at any time. All withdrawals from randomised treatment will be reported. If consent is given, any existing data or samples will be retained, and follow-up data will continue to be collected, and if not then a withdrawal form will be completed. The investigator may 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. All data will be analysed on an intention-to-treat basis.

Study Data

Data Management

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 chief investigator (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.

Database passwords

Database access will be strictly restricted through passwords to the authorised research team. The CI or delegate will request usernames and passwords 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, a personalised username and password will be requested via the CI or delegate.

Identifiable data

All participant contact information data will be stored on spreadsheets within the recruiting NHS 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. Participants will be identified on the study database using a unique code and initials. The investigator will maintain accurate patient records detailing observations on each patient enrolled.

Statistical Methods

Primary analysis

If the study continues to full recruitment analyses of effectiveness will be pragmatic, based on the intention-to-treat (ITT) sample**.** The significance level will be 5% (2 sided) for specified analyses. The estimated effect size and its precision (95% Confidence Intervals) will be presented for all outcomes. The main statistical analyses will establish the effectiveness of IVIG against standard therapy at 6 months post randomisation (see primary endpoints above). To this end linear mixed modelling (LMM) 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.

There is expected to be some missing data in the post treatment outcomes variables. The LMM analyses are based on maximum likelihood and will provide valid inferences under a missing at random (MAR) missingness mechanism

Secondary analyses

The secondary clinical assessments (EDSS, ASIA motor and sensory scales, SCI data sets, PedsQL, 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.

Exploratory moderator analyses

All analysis will be repeated considering age status (adult or child) as a moderator in interaction with treatment group (control or intervention), allowing estimates of treatment effect in the sub populations to be summarised.[23] We will carry out further explanatory analyses to assess the efficacy of the treatment within NMO or idiopathic TM diagnosis and further putative biological markers by allowing for interactions with treatment arm. When considering these moderator analyses, following established methods[24] we will centre and orthogonalise interaction terms.

Further information on the statistical analysis plan can be found in the protocol and Appendix 1.

Interim Futility Analysis

TM is a rare disease and therefore requires a multi-centre trial spanning several years, precluding recruitment to other interventional studies for this cohort. As such, an interim futility analysis will be performed after 6 months follow-up of 52 patients. If sample sizes are equal, the trial may be abandoned if the successes under the intervention treatment are fewer than under standard. The probability of abandoning the study at the interim analysis is 0.4449 if there is no difference between the treatment groups, and 0.0201 if treatment improves outcome. The primary trial statistician will remain blinded to the intervention and control group, and therefore an additional unmasked trial statistician will perform the interim

analysis. The results will be reviewed by the Data Monitoring Committee who have the ability to terminate the trial prematurely.

Economic Analysis

Drug pricing data and primary care, secondary care and social care costs will be calculated as previously described. Costs will be combined with the primary outcome measure in the form of a cost-effectiveness analysis. If IVIG results in higher costs and better outcome then an incremental cost-effectiveness ratio will be generated to show the extra cost incurred to achieve an extra unit of improvement. Due to uncertainty around results, cost-effectiveness planes and cost-effectiveness acceptability curves will be used, with bootstrapping of skewed results.

Long-term cost-effectiveness over a five- and ten-year period will be calculated using a Markov model. Response to treatment will be classified, and transition probabilities between groups will be derived from the six- and twelve-month follow-up data. Costs and QALYs for each category will be derived from the trial data. As limited data will be available on long term costs, we will conduct both deterministic and probabilistic sensitivity analyses.

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

There will be missing data in post treatment outcome variables as participants discontinue treatment or are lost to follow-up. Inferences will be valid provided the missing data generating mechanism is missing at random (MAR), and is not predicted by any variables in the model that is missingness is predicted only by variables that are included in the model.

Economic Evaluation

The use of IVIG, IVMP, additional treatments and rescue PLEX will be recorded throughout the follow-up period and costed using drug pricing data from the British National Formulary and the Department of Health. Use of primary care, secondary care and social care will be recorded at three, six and twelve month follow-ups using the CSRI, and costs calculated to determine total cost for control and treatment arms.

A cost-effectiveness analysis will be performed using the primary and secondary outcome measures of improvement in ASIA scores, and secondary outcome of QALYs with EQ-5D-Y, EQ-5D-5L and CSRI. If IVIG results in higher costs and better outcome, then an incremental cost-effectiveness ratio will be generated to show the extra cost incurred to achieve an extra unit of improvement.

Data monitoring

The Data Monitoring Committee (DMC) will review effectiveness and safety data during the trial to inform their recommendations to the Trial Steering Committee (TSC). The DMC is independent from the sponsor and funders, and will consist of a statistician, clinician and clinician scientist.

Harms

Most adverse drug reactions that occur in this study, whether serious or not, will be expected treatment-related side effects as IVIG has a well-established side effect profile. Monitoring and reporting of adverse events will be performed by the site PI and research team, and will be recorded on an eCRF and uploaded to the InferMed MACRO database. Serious adverse events will be reported to the sponsor in an expedited manner, who in turn will inform the CI. The CI will assess SUSAR status. If a SUSAR is detected, the CI will work with the sponsor to report to the regulatory authorities. The CI will report to relevant ethics committees and DMC.

An independent TSC and DMC will convene every 6 months, the TSC's key purpose will be to monitor study progress and act on the recommendations of the DMC. The DMC will aim to meet 3 weeks prior to the TSC convening. Increased frequency of meetings will be arranged depending on the requirements of the study DMC and TSC recommendations.

Auditing

Monitoring of this trial will ensure compliance with Good Clinical Practice (GCP). Scientific integrity will be managed and oversight retained, by the King's Health Partners Clinical Trials Office Quality Team. 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.

ETHICS AND DISSEMINATION

Ethical and safety considerations

This trial has approved by the United Kingdom National Research Ethics Service (NRES) committee (South Central - Berkshire B; REC 14/SC/1329). Clinical trial authorisation for a Type A trial has been granted via the Medicines and Healthcare Products Regulatory Agency (MHRA) notification scheme. Written approval from the respective Research and Development (R&D) departments will be obtained for each participating site.

The CI will ensure that this study (and all subsequent approved amendments) is conducted in accordance with the principles of the Declaration of Helsinki (1996), in full conformity with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines for GCP (CPMP/ICH/135/95 July 1996), the Research Governance Framework, and the Medicines for Human Use (Clinical Trial) Regulations 2004. Pharmacovigilance will be monitored by the CI. The CI will report to the REC, MHRA and funders (NIHR) during and at the end of the trial.

All protocol modifications will be disseminated to all relevant parties.

Informed Consent

A member of the trial staff will screen the patient, and if eligible, patients will be given age appropriate patient information sheets (PIS) explaining the trial (see Appendix 2). Trial staff will obtain informed written consent from patients over 16 years of age wishing to participate. For those aged under 16, assent will be obtained from the patient and consent from the parents or legal guardian. At the same time consent will be obtained for the storage and use of participant data and biological specimens in future studies.

Confidentiality

Only anonymised data will be entered onto the eCRF. Source data will be retained on password-protected Trust computers and in patient notes to protect patient confidentiality.

Access to Data

The CI will control access to data.

Dissemination plan

Study findings will be presented in conferences and published in peer reviewed journals.

ACKNOWLEDGEMENTS

Members of TSC (R Hughes, M Lim, A Jacobs, C Lundy, B Babcock, L Gray, M Kappler, and M Sanders) and DMC (J Zajicek, S Cotterill, and A Parker); the Transverse Myelitis society, Guthie Jackson Charitable Foundation, and UK Children's Neurological Research Campaign (UKCNRC) for early support through trial design and subsequent grant applications. We are thankful to Carla Rush and Rosemary Howe for supporting the trial group on various aspects of the application. This study is also supported by the United Kingdom Clinical Research Collaboration-registered King's Clinical Trials Unit at King's Health Partners, which is part funded by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London and the NIHR Evaluation, Trials and Studies Coordinating Centre.

Collaborating Principle Investigators: Absoud M*, Brex PA*, Constantinescu C, Duddy M, Forrest K, Galea I, Giovannoni G*, Hemingway C, Jacob A*, Jacob S, Kneen R, Lim M (Chief Investigator), Murray K, Palace J*, Pike M*, Ramesh V*, Robertson N, Rog D, Vijayakumar K, Wassmer E, te Water Naude J, West S, Whitehouse W, Williams V.
* Denotes co-authors.

Centres: Children's Neurosciences, Evelina Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, London (M.L., M.A.); Department of Neurology, Guy's and St Thomas' NHS Foundation Trust, London (V.W.); Department of Neurology, King's College Hospital NHS Foundation Trust, London (P.B.); Department of Paediatric Neurology, Great Ormond Street Hospital Foundation Trust, London (C.H.); Centre for Neuroscience and Trauma, Blizard Institute, University of London and Bart's Health NHS Trust, London (G.G.); Department of Paediatric Neurology, Alder Hey Children's Hospital NHS Foundation Trust, Liverpool (R.K.); The Walton Centre, Walton Centre NHS Foundation Trust, Liverpool (A.J.); Department of Paediatric Neurology, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford (M.P.); Department of Neurology, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford (J.P.); Department of Paediatric Neurology, Birmingham Children's Hospital NHS Foundation Trust, Birmingham (E.W.); Department of Neurology, University Hospital Birmingham NHS Trust, Birmingham (S.J.); Department of Paediatric Neurology, University Hospital of Wales, Cardiff and Vale NHS Trust, Cardiff (J.W.N.); Department of Neurology, University Hospital of Wales, Cardiff and Vale NHS Trust, Cardiff (N.R.); Department of Paediatric Neurology, North Bristol NHS

Trust, Bristol (K.V.); Department of Neurology, University Hospital Bristol NHS Foundation Trust, Bristol; Department of Paediatric Neurology, Royal Manchester Children's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester (S.W.); Department of Neurology, Salford Royal NHS Foundation Trust, Salford (D.R.); Department of Paediatric Neurology, University Southampton NHS Trust, Southampton (K.F); Department of Neurology, University Southampton NHS Trust, Southampton (I.G.); Department of Paediatric Neurology, Great Northern Children's Hospital, Newcastle Hospitals NHS Foundation Trust, Newcastle (V.R.); Department of Neurology, Newcastle Hospitals NHS Foundation Trust, Newcastle (M.D.); Department of Paediatric Neurology, Nottingham University Hospitals NHS Trust, Nottingham (W.W.); Department of Neurology, Nottingham University Hospitals NHS Trust, Nottingham (C.C.); Department of Neurology, University of Edinburgh, NHS Lothian (K.M.).

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: IVIG is provided by Biotest AG, Germany, and should any commercial opportunity arise the industrial partner has an option to an exclusive licence from the sponsor (Guy's and St Thomas' NHS Foundation Trust) and potential for a revenue sharing arrangement in the event of a commercial outcome; OC serves as consultant for Novartis, Biogen, and GE Healthcare, GG has received consultation and speaking fees from Biogen-Idec, GSK, Merck-Serono, Novartis, Genzyme-Sanofi and Synthon BV, ML has received consultation fees from CSL Behring, received travel grants from Merck Serono, and been awarded educational grants to organize meetings by Novartis, Biogen Idec, Merck Serono and Bayer, JP has performed advisory work for Biogen Idec, Merck Serono Ltd, Bayer Schering Pharma, Novartis Pharmaceuticals UK Ltd, Teva Pharmaceutical Industries Ltd, Gilenya, Ono Pharmaceutical Co Ltd, Primary i-research, Alexion, Chugai Pharma Europe, receives research support from the Merck Serono Ltd, Bayer Schering Pharma, Biogen Idec and Teva, and received conference expenses from Novartis, Merck Serono and Biogen Idec, MP has received a meeting support grant from Euroimmun; MA serves on the data safety monitoring board for a study sponsored by Neurim Pharmaceuticals and is on the editorial advisory board for the *International Journal of Language & Communication Disorders*, OC is an Associate Editor of *Neurology*, GG is on the steering committee for studies sponsored by AbbVie, Biogen-Idec, Novartis, Teva and

Roche, AJ is supported by the NHS National Specialised Commissioning Group for NMO, JP serves on the scientific advisory board for the Charcot Foundation.

PB, JG, JH, JK, CM, PM, AP and NR have no conflicts of interest to declare.

FUNDING STATEMENT

This project was funded by the National Institute for Health Research, Health Technology Assessment (project number 11/129/148), with IVIG supplied by an industrial partner, Biotest AG, Germany. Should any commercial opportunity arise the industrial partner has an option to an exclusive licence from the sponsor (Guy's and St Thomas' NHS Foundation Trust) and potential for a revenue sharing arrangement in the event of a commercial outcome. The study sponsor and funders had no role in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, nor will they have ultimate authority over any of these activities.

Department of Health Disclaimer:

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Health Technology Assessment, NIHR, NHS or the Department of Health.

Authors' contribution:

The study design and protocol was conceptualised by ML, MA and AJ. All co-authors contributed significantly to the conception and design of the study, with specific additional contributions from each co-author within their area of expertise; adult clinical neurology research (PB, JP, AJ, NR), paediatric clinical neurology research (MP, MA, ML), neuroimaging (OC), immunobiology (GG, NR), trial methodology (JK, CM), statistics (JH, AP) and health economics (PM).

JG prepared the early drafts of the manuscript; and developed with input from JH, ML and MA. All authors critically reviewed all versions of the manuscripts, and approved the final version.

Exclusive Rights Statement:

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	____3, Appendix 1
	2b	All items from the World Health Organization Trial Registration Data Set	____Appendix 1
Protocol version	3	Date and version identifier	____3, Appendix 1
Funding	4	Sources and types of financial, material, and other support	____3, 20, 21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____19_____
	5b	Name and contact information for the trial sponsor	____Appendix 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__21, Appendix 1
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____Appendix 1

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	____5,6_____
	6b	Explanation for choice of comparators	____5,6_____
Objectives	7	Specific objectives or hypotheses	____6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	____7,12,14,15

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	____7, Appendix 1
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	____7,8_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____8_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____8,13_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8 (inpatient treatment)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____8_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____9_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____9,10,11___

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___11,12_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___12_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____12_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____12_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____12_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____N/A (treatment will be unblinded)
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___13, Appendix 1
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____13_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____13_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____14,15, Appendix 1
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	____14,15_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	____13,14,15,16_
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__16, Appendix 1
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____15_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____17_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____17_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____17,18____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____18_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___18, Appendix 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___18, Appendix 2
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	___18, 14_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___20,21_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___18_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____18_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____2_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	____18_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____Appendix 2_
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	____Appendix 3_

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

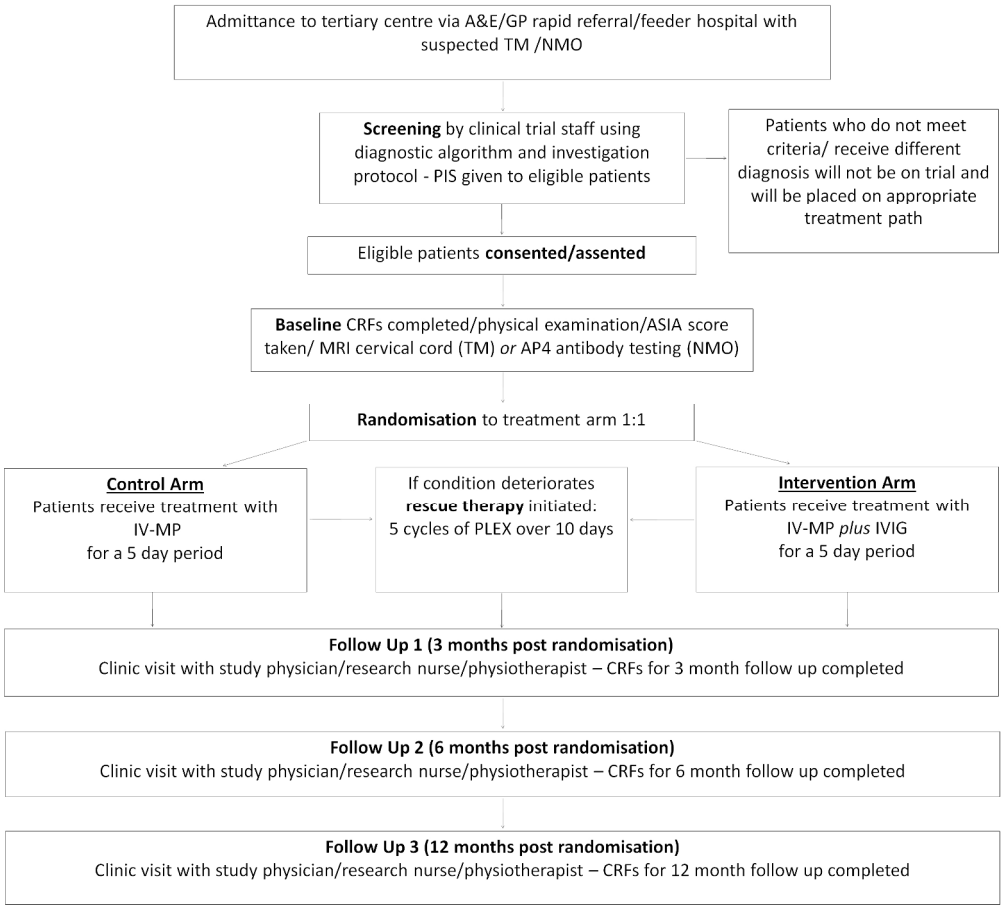


Figure 1: Flow chart showing the process of patient recruitment, treatment and follow-up.
270x243mm (300 x 300 DPI)

ADMINISTRATIVE INFORMATION

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

Trial Acronym: STRIVE

Trial Registration: This study is registered with EudraCT (REF: 2014-002335-34); and ISRCTN (REF: 12127581).

Data category	Information
Primary registry and trial identifying number	EudraCT (REF: 2014-002335-34)
Date of registration in primary registry	03/06/2014
Secondary identifying numbers	ISRCTN (REF: 12127581)
Source(s) of monetary or material support	This project was funded by the National Institute for Health Research, Health Technology Assessment (project number 11/129/148). IVIG was supplied by an industrial partner, Biotest AG, Germany.
Primary sponsor	Guy's and St Thomas' NHS Foundation Trust
Contact for public queries	Ms Rosemary Howe, Clinical Trial Manager, King's Clinical Trials Unit, IoPPN PO64 (M3.21), King's College London, De Crespigny Park, Denmark Hill, London, SE5 8AF [02078485996] [rosemary.howe@kcl.ac.uk]
Contact for scientific queries	Dr Ming Lim, Children's Neurosciences, Evelina Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, London. [02071887188] [ming.lim@gstt.nhs.uk]
Public title	STRIVE: A multicentre randomi**S**ed controlled **TR**ial of

Data category	Information
	Intra**VE**nous immunoglobulin (IVIG) versus standard therapy for the treatment of transverse myelitis in adults and children
Scientific title	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
Countries of recruitment	United Kingdom
Health condition(s) or problem(s) studied	Transverse myelitis (TM) (acute, first onset cases), including first presentation of neuromyelitis optica (NMO)
Intervention(s)	Active comparator: IVIG (2g/kg in divided daily doses) and methylpredniosolone (30mg/kg/day or 500mg/m^2/day up to 1g/day, for 5 days) Standard treatment: Methylpredniosolone (30mg/kg/day or 500mg/m^2/day up to 1g/day, for 5 days)
Key inclusion and exclusion criteria	**Ages eligible for study:** ≥1 years **Sexes eligible for study:** both **Inclusion criteria:** 1. Diagnosis of 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 MS (McDonald 2010 space criteria) • Progression to nadir between 4 h and 21 days) OR Have been diagnosed with first presentation of neuromyelitis optica.

Data category	Information
	(Patients with definite modified NMO will meet the following criteria (Wingerchuck et al, 2006). • Absolute criteria, both: i. Optic neuritis ii. 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) 2. Have an ASIA Impairment score of A, B or C 3. 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 4. Give assent(<16 years)/consent to participate in the trial **Exclusion Criteria:** 1. Contraindication to IVIg as stated in the product SmPC, or receiving IVIg for other reasons 2. Previously known systemic autoimmune disease (eg systemic lupus erythematosus) or any evidence of systemic inflammation during current presentation. 3. Direct infectious aetiology (eg varicella zoster) 4. Previous episode of CNS inflammatory demyelination 5. Acute disseminated encephalomyelitis (ADEM) 6. Other causes of myelopathy not thought to be due to myelitis (eg nutritional, ischaemic, tumour etc.) 7. Other disease which would interfere with assessment of outcome measures 8. Known pregnancy

Data category	Information
	9. Circumstances which would prevent follow-up for 12 months
Study type	Interventional Allocation: randomised Intervention model: parallel assignment Masking: single blind (investigator, outcomes assessor) Primary purpose: treatment Phase III
Date of first enrolment	March 2015
Target sample size	170
Recruitment status	Recruiting
Primary outcome(s)	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.
Key secondary outcomes	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 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

Data category	Information
	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

Protocol Version: v3.0, 15/01/2015

Funding: This project was funded by the National Institute for Health Research, Health Technology Assessment (project number 11/129/148), with IVIG supplied by an industrial partner, Biotest AG, Germany. Should any commercial opportunity arise the industrial partner has an option to an exclusive licence from the sponsor (Guy's and St Thomas' NHS Foundation Trust) and potential for a revenue sharing arrangement in the event of a commercial outcome. The study sponsor and funders had no role in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, nor will they have ultimate authority over any of these activities.

Department of Health Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Health Technology Assessment, NIHR, NHS or the Department of Health.

Roles and Responsibilities:

Protocol Contributors: M Absoud, PA Brex, O Cirrarelli, G Giovannoni, J Hellier, A Jacob, J Kelly, M Lim, P McCrone, C Murphy, J Palace, A Pickles, M Pike, N Robertson; and the transverse myelitis (TM) society. Subsequent trial amendments were made following feedback from the Data Monitoring Committee (J Zajicek, S Cotterill and A Parker), Trial Steering Committee (R Hughes, M Lim, A Jacobs, C Lundy, B Babcock, L Gray, M Kappler, and M Sanders), and all Principle Investigators (M Absoud, P Brex, C Constantinescu, M Duddy, K Forrest, I Galea, G Giovannoni, C Hemingway, S Jacob, R Kneen, K Murray, J

Palace, M Pike, V Ramesh, N Robertson, D Rog, K Vijayakumar, E Wassmer, J te Water Naude, S West, W Whitehouse, V Williams.)

Trial Sponsor: Guy's and St Thomas' NHS Foundation Trust.

Trial Funder: The study is funded by the National Institute for Health Research (NIHR) Health Technology Appraisal Programme (ref 11/129/148). Biotest AG will provide the study drugs.

The study sponsor and funders have not had any role in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, and do not have ultimate authority over any of these activities.

Composition, roles, and responsibilities of the coordinating centre, steering committee, data management team, and other individuals or groups overseeing the trial.

Co-ordinating Centre: Guy's and St Thomas' NHS Foundation Trust
Trial Steering Committee: Prof Richard Hughes (Honorary Chair); Ming Lim - CI and Anu Jacobs - PI (Members); Claire Lundy – Paediatric Neurologist, Barbara Babcock – TM Society, Lew Gray – TM Society, Martin Kappler – Statistician, and Mark Sanders - Clinician (Independent Members).
Data Managing and Ethics Committee (DMEC): Prof John Zajicek (Honorary Chair); Sarah Cotterill – Statistician and Alasdair Parker - Clinician (Members).

Study Centres:
We completed a pre-trial pilot to assess feasibility, variations in local practice, and margins of clinical effectiveness. The following centres have agreed to participate in this study:

Children's Neurosciences, Evelina Children's Hospital at Guy's and St Thomas' NHS Foundation Trust, London; Department of Neurology, Guy's and St Thomas' NHS Foundation Trust, London; Department of Neurology, King's College Hospital NHS Foundation Trust, London; Department of Paediatric Neurology, Great Ormond Street Hospital Foundation Trust, London; Centre for Neuroscience and Trauma, Blizard Institute,

University of London and Bart's Health NHS Trust, London; Department of Paediatric Neurology, Alder Hey Children's Hospital NHS Foundation Trust, Liverpool; The Walton Centre, Walton Centre NHS Foundation Trust, Liverpool; Department of Paediatric Neurology, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford; Department of Neurology, John Radcliffe Hospital, Oxford University Hospitals NHS Trust, Oxford; Department of Paediatric Neurology, Birmingham Children's Hospital NHS Foundation Trust, Birmingham; Department of Neurology, University Hospital Birmingham NHS Trust, Birmingham; Department of Paediatric Neurology, University Hospital of Wales, Cardiff and Vale NHS Trust, Cardiff; Department of Neurology, University Hospital of Wales, Cardiff and Vale NHS Trust, Cardiff; Department of Paediatric Neurology, North Bristol NHS Trust, Bristol; Department of Neurology, University Hospital Bristol NHS Foundation Trust, Bristol; Department of Paediatric Neurology, Royal Manchester Children's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Manchester; Department of Neurology, Salford Royal NHS Foundation Trust, Salford; Department of Paediatric Neurology, University Southampton NHS Trust, Southampton; Department of Neurology, University Southampton NHS Trust, Southampton; Department of Paediatric Neurology, Great Northern Children's Hospital, Newcastle Hospitals NHS Foundation Trust, Newcastle; Department of Neurology, Newcastle Hospitals NHS Foundation Trust, Newcastle; Department of Paediatric Neurology, Nottingham University Hospitals NHS Trust, Nottingham; Department of Neurology, Nottingham University Hospitals NHS Trust, Nottingham; Department of Neurology, University of Edinburgh, NHS Lothian.

ASSESSMENT TRAINING

Assessors will be required to provide documentary evidence of satisfactory completion of training in the primary endpoint, ASIA Sensory and Motor Scoring (see: http://lms3.learnshare.com/home.aspx). In addition, assessors will be required to complete training manuals and CD's together with exam sheets for secondary outcome measures of Kurtzke's Functional Systems and Expanded Disability Status Scale which will be provided to each study site.

INTERVENTIONS

Chart detailing dosing of IVIG according to weight. Doses vary by day to minimise drug wastage.

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

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

STATISTICAL ANALYSIS

All analyses will follow the intention to treat (ITT) principle and the statistician will remain blinded. 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.[1]

A futility analysis will be undertaken after recruitment of 52 patients. If sample sizes are equal, this occurs if the successes under new treatment are fewer than under standard. The probability of abandoning the study at the interim analysis is 0.4449 if there is no difference between the treatment groups, and 0.0201 if treatment improves outcome.

If the study continues to full recruitment the final analyses of effectiveness will be conducted once the trial database has closed. 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.

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. Mixed effects logistic regression will be employed using binary outcome variable measured at the post treatment time points (3, 6 or 12 months).

The secondary clinical assessments with repeated measurements will also be analysed within a linear mixed model framework. Those measures with one follow up assessment will be evaluated with a general linear model. Stratification factors and treatment groups will feature as covariates.

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

REFERENCES:

1. White IR, Horton NJ, Carpenter J, et al. Strategy for intention to treat analysis in randomised trials with missing outcome data. BMJ 2011;342:d40

Patient Information Sheet for Adults

STRIVE: A multicentre randomiSed controlled TRial of IntraVEnous immunoglobulin (IVIg) versus standard therapy for the treatment of transverse myelitis in adults and children

Invitation

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the information below carefully:
Part 1 tells you the purpose of this study and what will happen to you if you take part
Part 2 gives you more detailed information about the conduct of the study

One of our team will go through the information sheet with you and answer any questions you have, and you may talk to others about the study if you wish.

PART 1

Why have I been asked to take part?

You have been chosen because you have developed either transverse myelitis (TM) or neuromyelitis optica (NMO).

TM is a rare nervous system disorder where the coating (myelin) of nerve cells in the spinal cord become inflamed, affecting the transmission of signals along the cord. TM can also sometimes develop as part of NMO, a nervous system disorder which also affects vision. TM and NMO can affect both adults and children.

In TM, signals to the body below the inflamed area of the spinal cord can be affected producing symptoms including muscle spasms, muscle weakness and lower back pain. The person may have odd sensations of the skin and soft tissue including tingling, numbness, coldness, burning or hypersensitivity to touch. In some people, loss of bladder or bowel function and paralysis occur. In NMO, as the optic nerve can be affected, the most prominent symptom is a blurring or loss of vision. Symptoms develop over hours, days, or weeks and the causes are not well understood. They may be linked to an autoimmune response, when the immune system mistakenly attacks body tissues.

As TM and NMO are rare diseases, little is known about the causes, mechanisms and best treatment routes – it is thus important that we do more research, and this study aims to investigate what is the most effective treatment. Every child or adult in your region affected by TM or NMO will be invited to take part in this study and we hope to include 170 people.

What is the purpose of the research project?

When people suffer from an attack of TM or NMO, many recover well having maybe some muscle weakness, or poor vision in NMO. At the moment, we cannot always predict what the future holds for those affected, but we think that the sooner patients get treatment, the less damage is done to their nerves and the better their recovery. There are several treatments available, but different hospitals use different ones. We would like to investigate if a combination treatment is better than the most common standard treatment used.

We will not be using any new medicines. All are used regularly in hospitals and are already used in TM and NMO. The drugs are intravenous methylprednisolone (IV-MP) which is a corticosteroid and intravenous Immunoglobulin (IVIg), which both suppress inflammation. The study does not involve using a placebo or dummy treatment; everyone will receive the standard treatment (IV-MP), so at the very least you will receive standard care for your illness.

If after initial treatment your doctor and you think that there has not been enough improvement, different treatments such as plasma exchange (which involves replacing the plasma in your blood) may be considered.

<u>The study aims to:</u>

1. Find out if different treatments give different results.
2. See how these treatments affect quality of life, wellbeing, participation and behaviour over time.
3. Aid future research by collecting and storing blood and spinal fluid samples for future studies. These samples will be taken at the same time as samples which the hospital takes as part of routine investigations.
4. Ultimately, produce a treatment 'gold standard', providing a set of assessments to aid diagnosis and a tested treatment plan.

Do I have to take part?

The answer is no, it is up to you to decide whether or not to take part. Also, if you do decide to take part, you are free to withdraw from the research at any time, you do not even have to give your reasons. Whatever your decision, or even if you join but later chose to withdraw, it will not affect the standard of care you will receive. Furthermore, if for any reason you lose the capacity to consent/withdraw, you will automatically be withdrawn from the study. In all cases of withdrawal, any data or samples already collected with consent, would be retained and used in the study.

What do I have to do if I agree to take part?

<u>The consent/assent process</u>

Once your have read this leaflet and have had any questions answered by our research team, if you are happy to take part you will be asked to sign a consent form. You will be given a copy of the consent form plus this information sheet to keep for your records.

The care you will receive in hospital will be very similar to that of any patient with acute TM or NMO, with the addition of some extra examinations, some study questionnaires, an MRI scan and some extra blood and spinal fluid samples for storage in our Biobank.

Assessments
The doctor will perform some physical assessments and tests on you, mainly tests that all patients with TM undergo.

Clinical Data and Questionnaires
The doctor will collect information about your normal health, family history, and you current illness and its onset. There will also be some study specific forms and questionnaires to complete; this should take about 30-45 minutes.

MRI scans
MRI uses a magnet to make medical pictures of the body and it allows us to see which areas of the brain or spinal cord have inflammation. The scan is part of the care given to all patients with TM or NMO, so if you have already had a scan during this admission, the research team would like to look at a copy of this. If not, one will be arranged for you.

Bloods and Spinal Fluid Samples
A sample of your blood (via venepuncture) and your cerebrospinal fluid or CSF (via lumbar puncture) will be taken for the purpose of the study and biobanked. You will NOT undergo any *additional* procedures to obtain these samples, we will only ask for extra samples to be taken during routine hospital venepuncture/lumbar puncture. We would like you to know that:

- Blood and spinal fluid samples are taken in all cases of TM as part of routine hospital investigations.
- Your study samples will be stored in a registered Human Tissue Act licensed biobank (a secure place for future use). Further studies will ensure a high standard of research review by the study team.
- One such study may be for future DNA analysis. DNA (deoxyribonucleic acid), is found in all cells of the body, and contains the genetic information for the development and working of human beings. Analysing blood samples will allow future research to find out the relationship between our environment (exposures) and our personal susceptibility (genes). We may also come up with better diagnostic tests. If in the future we do find something interesting in analysis of the DNA, we will ask for an extra blood sample to check our findings. We will also try to repeat our findings in a clinical laboratory that undertakes genetic tests, if you would like and if this is possible. Sometimes, our findings might need more tests in the laboratory to know if they are relevant or not. Any results are research findings and are not a clinical test.

Randomisation and Treatment
Once we have collected all the above baseline information (pre-treatment information), you will be randomised to one of two treatment arms/groups. Randomisation ensures that both groups are the same to start with, so that the different treatments can be compared fairly. You have a 50% chance of going into either treatment arm.

Treatment arm 1 will receive the standard hospital treatment for demyelination, intravenous methylprednisolone (IV-MP), for a period of 5 days.

Treatment arm 2 will receive standard therapy with IV-MP for 5 days *plus* treatment with intravenous immunoglobulin (IVIg) for 5 days.

Unlike some studies, the doctors will not be 'blinded', meaning that they will know which treatment your will be receiving, and you will also be allowed to know.

Follow Up

Once treatment is complete and you have left hospital, we would like to monitor your progress. We will do this during your routine follow-ups in clinic, at 3 months, 6 months and 12 months, and it will take the form of study assessments and questionnaires. These assessments will chart your physical recovery, but clinical questionnaires will also give us information on factors such as you progress, quality of life and wellbeing. At the 6 month visit, if routine blood samples are being requested, we will also take another biobank sample. Each visit will take about 1 hour. These visits will be conducted by staff who will not know which treatment you received (so that they will be unbiased with the results of your assessment) – we will ask you not to tell the assessor which treatment arm you were on. At the last visit, we will ask whether we can contact you in the future to take part in other studies.

What are the possible disadvantages and risks of taking part?

We foresee no additional risks by taking part in the study, as all medications are already used in general practice, there are no placebos, and as a minimum, *every* patient will receive standard care given in hospitals for their illness.

If you should receive IVIg treatment, there are some common side effects, but these are transient and can occur in any patient taking IVIg, for any condition. These can include: chills, headache, fever, palpitations, nausea and vomiting, allergic reactions, infusion related reaction, low blood pressure and mild back pain or joint pain. Your doctor will talk to you further about these if you require.

During treatment on either arm of the trial, if your doctor does not think that there has been enough improvement in your condition, additional treatment with plasma exchange (PLEX) will be considered as a 'rescue therapy'. PLEX involves replacing the plasma in a person's blood. The possible use of a rescue therapy has been built into study procedure, and means that if it is required, it will not affect your study status.

What are the possible benefits of taking part?

We cannot promise that participation in this study will provide extra benefits. We do hope, however, that the information provided will help further improve treatment for people with TM in the future.

PART 2

What if there is a problem whilst I am on the study?

If you have a concern about any aspect of this study, you should ask to speak to the researchers, who will do their best to answer your questions. Please contact: <NAME>, Principal Investigator, at (insert email): XXXXX or by calling (insert telephone no) XXXXX.

If you have a complaint, you should talk to your research doctor who will do their best to answer your questions. If you remain unhappy, you can make a formal complaint through the NHS complaints procedure. Details can be obtained through the Guy's and St Thomas' Patient Advisory Liaison Service (PALS) on 0207 1887188, address: PALS, KIC, Ground floor, north wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH .
This study is insured by Guy's & St Thomas' NHS Foundation Trust under the Clinical Negligence Scheme for trials.

All professional staff involved in the study hold professional indemnity to work within Guy's and St Thomas' NHS Trust. In the event that you are harmed during the research and this is due to negligence then you may have grounds for legal action for compensation against Guy's and St Thomas NHS Trust but you may have to pay your legal costs. The normal NHS complaints mechanisms are still available to you.

Will my participation in the research project be kept confidential?

Yes. All the information about your participation in this study will be kept confidential in accordance with the Data Protection Act 1998. The information from each patient will be stored in a confidential database, where it will be identified only by a unique PIN number.

Involvement of the General Practitioner/Family doctor (GP)

Your GP will be notified of your participation in the trial, and will receive a copy of the consent form.

Will any genetic tests be done?

No specific genetic tests will be carried out.

What will happen to the results of the research study?

It is intended that the results will be published in a reputable medical journal; you will not be identified in any report/publication. The results of the study will also be presented in National and International meetings. If you would like a summary of the final results, this will also be made available.

Who is organising and funding the research?

The research is being funded by the National Institute for Health Research (NIHR.ac.uk) and is organised by a research team from the King's Clinical Trials Unit and the Evelina Children's Hospital in London, as part of the King's Health Partners Academic Health Science Centre.

Who has reviewed the study?

The study also has ethical approval from The South-Central Berkshire B Research Ethics Committee and approval from your local hospital's Research & Development Department.

If you have any questions about this study, then please contact the study team members at: <INSERT LOCAL PHONE NUMBER>

Alternatively, if you would like to discuss your participation in the study with someone outside of the study team, you may wish to approach the local Patient Advisory Liaison Service (PALS) on <*INSERT LOCAL PALS NUMBER*>.

Thank you for taking the time to read this information sheet

Information sheets for children aged 6-11

A study of the best treatment for transverse myelitis (TM

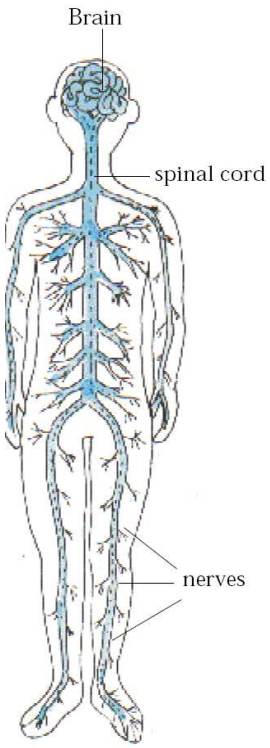
Invitation to take part

You are being invited to take part in a research study. Before you decide if you want to join in, it is important to understand why the research is being done and what it will involve for you. Read through this leaflet and then talk about it with your family, friends, doctor or nurse if you want to.

Why have I been asked to take part?

You are not feeling very well at the moment, you might have heard the doctor say transverse myelitis, but we can just call it TM, or a type of TM called neuromyelitis optica, which we can shorten to NMO. We will ask about 170 people (children and adults) with these illnesses to join in the study.

What are TM and NMO?



The brain is like a computer that sends messages to your body telling it what to do - like "walk" or "talk."

The spinal cord is like a thick bunch of wires attached to the brain. Messages travel from the brain along the spinal cord to the muscles all around your body.

Therefore, if your brain wants your arm to lift up and wave, it sends a message along your spinal cord to your arm. Your arm gets the message and starts to wave!

When a person has TM, the covering that protects the nerves in the spinal cord is affected, so the messages cannot always get through.

In TM, most of the problems are in the spinal cord. If you have TM, you may have symptoms like weak muscles or strange feelings in your skin like tingling, numbness or extreme hot or cold. You may also find it difficult to go to the toilet.

In NMO (a type of TM), the same sort of damage is happening to spinal nerves and affecting messages, but there is also a problem with eyesight.

What is research and why is this project being done?

Research is trying to find the answers to questions (or problems) by carrying out tests. There are different treatments to help make children with TM get better, but we want to find out the one that is best?

Do I have to take part?

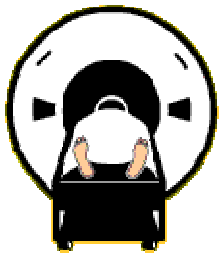
No - it is up to you. Moreover, if you do decide to take part but then change your mind later, you can tell your parents or nurse or doctor that you want to stop and you do not even have to tell us why if you do not want to. Nobody will be upset with you.

What will happen to me if I take part in the research?

If you are happy to take part, we need to get you and your parent/guardian to sign a form agreeing to take part. If you are between 8 and 11 years old, you can sign what is called an *Assent* form, whilst your parent(s) sign a *Consent* form. If you would like to take part but do not want to sign, you can just let your parent(s) sign the Consent form. If you are under 8, you do not have to sign any forms.

We will then ask you and your parents to answer some questions regarding your normal health, your family and how you feel at the moment. This will take about 45-60 minutes.

All children that come into hospital with TM need to have some examinations and tests done, and we can use these for our study.



One of these examinations will be an MRI scan, which you might have heard of. The MRI uses magnetic fields to create an image of the brain and spinal cord and shows patches of the brain that are affected by this type of illness.

Other types of tests that all hospitals have to do for TM are tests on your blood and spinal fluid. When the nurse takes these samples, we will be asking him or her to take a few extra ones at the same time for the study.

We would like to store some of these samples to use for future research.

Once we have all the information about you that we need, we will start you on one of two treatments:

- one treatment is with something we can just call IV-MP (its long name is intravenous methylprednisolone). You would be on this treatment for 5 days.

OR…

- the other treatment is with IV-MP *and* something we can call IVIg (whose long name is intravenous immunoglobulin). You would be on this treatment for up to 5 days.

These medicines (the IV-MP and IVIg) are given via a small tube into your vein called a cannula. This is the way they are usually given to patients and is not just for the study.

If you do get the IVIg, in some people it can have an effect on them, for example they can feel a bit sick, get a temperature, a headache or feel achy – let your doctor know if you get any new problems. Whichever treatment you get though, the medicines have already been used on children with TM all over the country, we are just researching which works best.

When your treatment is finished and you have left hospital, we would like to keep an eye on you to see how you are doing. We will do this by meeting you at 3, 6 and 12 months at your normal follow up appointments with the doctor. We will ask you and your parents or guardian some more questions.

All the information we collect about you will be stored safely. Nobody other than your doctor and the research team can find out about it.

Might anything about the research upset me?

If anything does worry you or you think things are not right, do not be worried about telling your parent(s) and the research team, and they will be able to help.

Will being part of this research help me?

We cannot promise being on this study will help you, but the information we get might help treat children with TM in the future. If you wish, when the study is finished, you and your parents can have a copy of the results – let us know if you would like to have these.

Thanks for reading this -
we hope you will join us in this study!

Information sheets for children aged 12-16

A study of the best treatment for transverse myelitis (TM)

Invitation

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the information below carefully:
Part 1 tells you the purpose of this study and what will happen to you if you take part
Part 2 gives you more detailed information about the conduct of the study

One of our team will go through the information sheet with you and answer any questions you have, and talk about it with your family, friends, doctor or nurse if you want to.

PART 1

Why have I been asked to take part?

You have been asked because you have developed an illness called transverse myelitis, but we can just call it TM, or you may have a form of TM called neuromyelitis optica, or NMO for short.

TM is a rare disease that affects the coating (myelin) of nerve cells in the spinal cord. Nerves are how we send messages around the body. In TM, damage is caused by inflammation (swelling) in the nerves of the spinal cord which means messages have trouble getting through. The cause may be an 'autoimmune' response - when your defence systems mistakenly start to attack your own body!

Because the messages are not getting through properly, it can produce symptoms, which can include muscle weakness and lower back pain. There may also be odd sensations such as tingling, numbness, coldness or burning or super-sensitivity to touch, or you might have problems going to the toilet. In NMO, as the nerves to the eyes can also be affected, the most noticeable symptom is a blurring or loss of vision Symptoms can develop over hours, days, or even weeks. It can affect both adults and children.

As TM is a rare disease, it is important that we do more research. Every child in your region affected by TM will be invited to take part in this study and we hope to include 170 children and adults.

What is the purpose of the research project?

Whilst many children with TM make a good recovery, some will be left with ongoing health care problems – we cannot always predict what will happen. We think that the sooner patients get treatment; the less damage is done to their nerves and the better their recovery. At the moment, different hospitals give different treatments, and we would like to investigate if there is one that works best.

We will not be using any new medicines, all are used regularly in hospitals and they are all already used in children with TM. One is called methylprednisolone (IV-MP) and one is an immunoglobulin (IVIg), and again we will just call them IV-MP and IVIg. Both of these medicines work to stop the swelling (inflammation) that affects the nerves. We would also like you to know that *every* child on the study will receive the standard initial treatment given in hospitals for these conditions, so there is no risk that you will do less well if you do take part.

We are asking if you would agree to take part in a research project and help to:

1. Find out if different treatments give different results.
2. See how these treatments affect children's quality of life, schooling, participation and behaviour over time?
3. Help in future studies - investigating for example why these illnesses occur, if we can predict them etc. - by letting us store some of your blood and spinal fluid for future studies. These samples will be taken at the same time as samples which the hospital takes as part of its normal investigations.
4. Ultimately, provide a 'gold standard' of treatment to guide all doctors, so that they can use it on children like you, knowing that they are giving the best care.

Do I have to take part?

No you do not – it is completely up to you! Ask the doctor or research staff, if you have any questions that are troubling you. And if you do decide to take part, **you are still free to stop taking part at any time during the research without giving a reason.** If you decide not to take part, or if you decide to stop at any time, this will not affect the care you receive.

What will happen to me if I take part?

The consent/assent process

If you are happy to take part, and are happy with the explanations from your research team and family, the first thing you and your parent/guardian will be asked to do is to give your consent – you can sign an Assent form and your parent(s) sign a Consent form. If you would like to take part but do not want to sign, you can just let your parent(s) sign the Consent form. You will be given a copy of this information sheet and your signed form to keep.

What will I be asked to do next?

Assessments

The doctor will do some assessment and tests on you, or he may already have performed these in which case we will just use the results. These will mainly be tests that all patients with demyelinating diseases undergo.

Questions about your illness

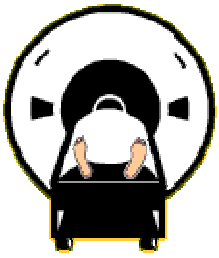
We will ask you and your parents/guardian to answer questions about your family history,

your health normally how you are feeling at the moment, and there will be some paper based assessments to complete. This will take about 45 minutes.

Bloods and Spinal Fluid

Before your start your treatment, and during your stay, the hospital will need to take samples of your blood and spinal fluid. When they take these samples, we will be asking them to take a few extra ones for the study, and we will keep these safe in a 'biobank' for future research.

MRI scans



Children with TM undergo an MRI scan as part of their investigation. The MRI uses magnetic fields to create an image of the brain and spinal cord and shows patches of the brain that are affected. The scan is part of the care given to children with TM – if you have already had a scan during this hospital visit, the research team would like to look at this scan.

Randomisation and Treatment

When we have collected all the pre-treatment information you will be randomised, (like flipping a coin), to one of two treatment groups. Randomisation ensures that both groups are the same to start with, so that the different treatments can be compared fairly. You have a 50% chance of going into either treatment group.

Treatment group 1 – the patient receives the standard hospital treatment for TM, which is IV-MP for 5 days.

Treatment group 2 – the patient receives standard therapy with IV-MP for 5 days *plus* treatment with IVIg for up to 5 days.

These medicines (the IV-MP and IVIg) are given via a small tube into your vein called a cannula. This is the way they are usually given to patients and is not just for the study.

Follow up

When your treatment is complete, we would like to monitor your progress. We will do one assessment before you leave hospital, but we would also see you at your routine follow-ups in clinic, at 3 months, 6 months and 12 months. At these clinic visits we will go through some assessments with you and also ask you to complete some questionnaires. At the 6 month visit, if routine blood samples are being requested, we will also take one more sample for the biobank. Each study visit will take about 45-60 minutes and will be carried out by someone who will not know which treatment you received (this is so they can be unbiased about the results of the assessments) – we will ask you not to tell them! On the last visit, we will ask whether we can contact you in the future to take part in other studies.

All your information will be stored in a confidential (private) database. The database is anonymous and will not have your name or personal details on it; instead you will be identified by a unique study number. Information on each patient will be updated during each clinic visit over the study period.

What are the possible risks benefits of taking part?

There are no extra risks if you take part in the study, and at the very least you will receive standard care for your illness. If you should receive IVIg treatment, there are some common side effects, but these are temporary and can occur in any patient taking IVIg, for any condition. These can include: chills, headache, fever, nausea and vomiting, allergic

reactions, palpitations, low blood pressure and mild back pain or joint pain. The doctor will talk to you further about this if you require.

During treatment, if your doctor does not think that there has been enough improvement in your condition, additional treatment with plasma exchange (PLEX) will be considered as a 'rescue therapy'. PLEX involves replacing some important components of a person's blood.

We cannot promise the study will provide extra benefits. We do hope, however, that the information you provide will help further improve treatment for young people with acute TM in the future. If you wish, when the study is finished, you and your parents can have a copy of the results – let us know if you would like to have these.

PART 2

What if there is a problem or something goes wrong?

If you have any worries or complaints during the study, you should share this with your parent(s) and the research team. Your parent(s) have been given details of who to call or how you could make a complaint in their Parent Information Sheets.

Will anyone else know I am doing this?

Yes, some people from the research team will see your medical notes to make sure the research is being done properly, and your family doctor will be told you are taking part.

Who is organising and funding the research?

The National Institute for Health Research is funding the research and it is being organised by a research team from the Evelina Children's Hospital in London.

Who has reviewed the study?

The study has been reviewed independently by expert panels and has been checked by an Ethics Committee, as is all research; they make sure that the research is OK to do. This study has been checked by the South-Central Berkshire B Research Ethics Committee.

How can I find out more?

You can ask members of the research team questions, you can speak to your parent/guardian or you can look at the study website: www.****.org.uk or phone us on *******.

If you would like to discuss your participation in the study with someone outside of the study team you may wish to approach the local Patient Advisory Liaison Service (PALS) on <*Insert local PALS number*>.

Thank you for reading this – please ask any questions if you need to.

Information sheets for parents/guardians

STRIVE: A multicentre randomiSed controlled TRial of IntraVEnous immunoglobulin (IVIg) versus standard therapy for the treatment of transverse myelitis in adults and children

Invitation

You and your child are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the information below carefully:
Part 1 tells you the purpose of this study and what will happen to you if you take part
Part 2 gives you more detailed information about the conduct of the study

One of our team will go through the information sheet with you and answer any questions you have, and you may talk to others about the study if you wish.

PART 1

Why has my child been asked to take part?

Your child has been chosen because he/she has developed either transverse myelitis (TM) or neuromyelitis optica (NMO).

TM is a rare nervous system disorder where the coating (myelin) of nerve cells in the spinal cord become inflamed, affecting the transmission of signals along the cord. TM can also sometimes develop as part of NMO, a nervous system disorder which also affects vision. TM and NMO can affect both adults and children.

In TM, signals to the body below the inflamed area of the spinal cord can be affected producing symptoms including muscle spasms, muscle weakness and lower back pain. The person may have odd sensations of the skin and soft tissue including tingling, numbness, coldness, burning or hypersensitivity to touch. In some people, loss of bladder or bowel function and paralysis occur. In NMO, as the optic nerve is affected, the most prominent symptom is a blurring or loss of vision. Symptoms develop over hours, days, or weeks and the causes are not well understood. They may be linked to an autoimmune response, when the immune system mistakenly attacks body tissues.

As TM and NMO are rare diseases, little is known about the causes, mechanisms and best treatment routes – it is thus important that we do more research, and this study aims to investigate what is the most effective treatment. Every child or adult in your region affected by TM or NMO will be invited to take part in this study and we hope to include 170 people.

What is the purpose of the research project?

When people suffer from an attack of TM or NMO, many recover well, having maybe some muscle weakness, and in NMO poor vision. At the moment, we cannot always predict what the future holds for those affected, but we think that the sooner patients get treatment, the less damage is done to their nerves and the better their recovery. There are several treatments available, but different hospitals use different ones. We would like to investigate if a combination treatment is better than the most common standard treatment used.

We will not be using any new medicines. All are used regularly in hospitals and are already used in TM and NMO. The drugs are intravenous methylprednisolone (IV-MP), a corticosteroid and intravenous Immunoglobulin (IVIg), which both suppress inflammation. The study does not involve using a placebo or dummy treatment; everyone will receive the standard treatment (IV-MP), so at the very least your child will receive standard care for their illness.

If after initial treatment your doctor and you think that there has not been enough improvement, different treatments such as plasma exchange (which involves replacing the plasma in a person's blood) may also be considered.

The study aims to:

1. Find out if different treatments give different results.
2. See how these treatments affect children's quality of life, schooling, participation and behavior over time?
3. Aid future research by collecting and storing blood and spinal fluid samples for future studies. These samples will be taken at the same time as samples which the hospital takes as part of routine investigations.
4. Ultimately, produce a treatment 'gold standard', providing a set of assessments to aid diagnosis and a tested treatment plan.

Does my child have to take part?

The answer is no, it is up to you - and whenever possible your child - to decide whether to take part. You are both free to withdraw from the research at any time, you do not even have to give your reasons. Whatever your decision, or even if you join but later chose to withdraw, it will not affect the standard of care your child will receive. Furthermore, if a child is on the study but the parent/guardian loses the capacity to consent/withdraw, the patient would automatically be withdrawn from the study. In all cases of withdrawal, any data or samples already collected with consent, would be retained and used in the study.

What does my child have to do if we agree to take part?

The consent/assent process

Once your have read this leaflet and have had any questions answered by our research team, if you are happy to take part you will be asked to sign a consent form. If your child is between 8 and 16, is able to understand the research and is happy to take part, they can also sign an "assent" form at the same time. You will be given a copy of your consent/assent forms plus this information sheet to keep for your records.

The care your child will receive in hospital will be very similar to that of any child with acute TM or NMO, with the addition of some extra examinations, some study questionnaires, an MRI scan and some extra blood and spinal fluid samples for storage in our Biobank.

Assessments
The doctor will perform some physical assessments and tests on your child, mainly tests that all patients with TM undergo.

Clinical Data and Questionnaires
The doctor will collect information about your child's normal health, family history, and their current illness and its onset. There will also be some study specific forms and questionnaires to complete; this should take about 30-45 minutes.

MRI scans
MRI uses a magnet to make medical pictures of the body and it allows us to see which areas of the brain or spinal cord have inflammation. The scan is part of the care given to all patients with TM or NMO, so if your child has already had a scan during this admission, the research team would like to look at a copy of this. If a scan has not already been taken, we will arrange one for them.

Bloods and Spinal Fluid Samples
A sample of your child's blood (via venepuncture) and cerebrospinal fluid or CSF (via lumbar puncture) will be taken for the purpose of the study and biobanked. Your child will NOT undergo any *additional* procedures to obtain these samples, we will only ask for extra samples to be taken during routine hospital venepuncture/lumbar puncture. We would like you to know that:

- Blood and spinal fluid samples are taken in all cases of TM as part of routine hospital investigations.
- Your child's study samples will be stored in a registered Human Tissue Act licensed biobank (a secure place for future use). Further studies will ensure a high standard of research review by the study team.
- One such study may be for future DNA analysis. DNA (deoxyribonucleic acid), is found in all cells of the body, and contains the genetic information for the development and working of human beings. Analysing blood samples will allow future research to find out the relationship between our environment (exposures) and our personal susceptibility (genes). We may also come up with better diagnostic tests. If in the future we do find something interesting in analysis of the DNA, we will ask for an extra blood sample to check our findings. We will also try to repeat our findings in a clinical laboratory that undertakes genetic tests, if you would like and if this is possible. Sometimes, our findings might need more tests in the laboratory to know if they are relevant or not. Any results are research findings and are not a clinical test.

Randomisation and Treatment
Once we have collected all the above baseline information (pre-treatment information), your child will be randomised to one of two treatment arms/groups. Randomisation ensures that both groups are the same to start with, so that the different treatments can be compared fairly. Your child has a 50% chance of going into either treatment arm.

Treatment arm 1 will receive the standard hospital treatment for demyelination, intravenous methylprednisolone (IV-MP), for a period of 5 days.

Treatment arm 2 will receive standard therapy with IV-MP for 5 days *plus* treatment with intravenous immunoglobulin (IVIg) for up to 5 days.

Unlike some studies, the doctors will not be 'blinded', meaning that they will know which treatment your child is receiving, and you will also be allowed to know.

Follow Up

Once treatment is complete and you have left hospital, we would like to monitor your child's progress. We will do this during your routine follow-ups in clinic, at 3 months, 6 months and 12 months, and it will take the form of study assessments and questionnaires. These assessments will chart your child's physical recovery, but clinical questionnaires will also give us information on factors such as their progress, quality of life and wellbeing. At the 6 month visit, if routine blood samples are being requested, we will take another biobank sample. Each visit will take about 1 hour. The visits will be conducted by staff who will not know which treatment your child received (this is so they can be unbiased about the results of the assessments) – we will ask you not to tell the assessor which treatment arm your child was on. At the last visit, we will ask whether we can contact you in the future to take part in other studies.

What are the possible disadvantages and risks of taking part?

We foresee no additional risks by taking part in the study, as all medications are already used in general practice, there are no placebos, and as a minimum, every child will receive standard care given in hospitals for their illness.

If your child should receive IVIg treatment, there are some common side effects, but these are transient and can occur in any patient taking IVIg, for any condition. These can include: chills, headache, fever, palpitations, nausea and vomiting, allergic reactions, infusion related reaction, low blood pressure and mild back pain or joint pain. The doctor will talk to you further about these if you require.

During treatment on either arm of the trial, if your doctor does not think that there has been enough improvement in your child's condition, additional treatment with plasma exchange (PLEX) may be considered as a 'rescue therapy'. PLEX involves replacing the plasma in a person's blood. The possible use of a rescue therapy has been built into study procedure, and means that if it is required, it will not affect your child's study status.

What are the possible benefits of taking part?

We cannot promise that participation in this study will provide extra benefits. We do hope, however, that the information provided will help further improve treatment for young people with TM in the future.

PART 2

What if there is a problem whilst we are on the study?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Please contact: <NAME>, Principal Investigator, at (insert email): XXXXX or by calling (insert telephone no) XXXXX.

If you have a complaint, you should talk to your research doctor who will do their best to answer your questions. If you remain unhappy, you can make a formal complaint through the NHS complaints procedure. Details can be obtained through the Guy's and St Thomas' Patient Advisory Liaison Service (PALS) on 0207 1887188, address: PALS, KIC, Ground floor, north wing, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH . This

study is insured by Guy's & St Thomas' NHS Foundation Trust under the Clinical Negligence Scheme for trials.

All professional staff involved in the study hold professional indemnity to work within Guy's and St Thomas' NHS Trust. In the event that you are harmed during the research and this is due to negligence then you may have grounds for legal action for compensation against Guy's and St Thomas NHS Trust but you may have to pay your legal costs. The normal NHS complaints mechanisms are still available to you.

Will my child's taking part in the research project be kept confidential?

Yes. All the information about your child's participation in this study will be kept confidential in accordance with the Data Protection Act 1998. The information from each patient will be stored in a confidential database, where it will be identified only by a unique PIN number.

Involvement of the General Practitioner/Family doctor (GP)

The family GP will be notified of your child's participation in the trial, and will receive a copy of the assent/consent form.

Will any genetic tests be done?

No specific genetic tests will be carried out.

What will happen to the results of the research study?

It is intended that the results will be published in a reputable medical journal. Your child will not be identified in any report/publication. The results of the study will also be presented in National and International meetings. If you would like a summary of the final results, this will also be made available.

Who is organising and funding the research?

The research is being funded by the National Institute for Health Research (NIHR.ac.uk) and is organised by a research team from the King's Clinical Trials Unit and the Evelina Children's Hospital in London, as part of the King's Health Partners Academic Health Science Centre.

Who has reviewed the study?

The study also has ethical approval from The South-Central Berkshire B Research Ethics Committee and approval from your local hospital's Research & Development Department.

If you have any questions about this study, then please contact the study team members at: <INSERT LOCAL PHONE NUMBER>

Alternatively, if you would like to discuss your participation in the study with someone outside of the study team, you may wish to approach the local Patient Advisory Liaison Service (PALS) on <*INSERT LOCAL PALS NUMBER*>.

Thank you for taking the time to read this information sheet

Centre Number: _____

Patient Identification Number for this trial: _____

ASSENT FORM FOR CHILDREN

(To be completed by the Child/Young Adult 8-16)

Name of Patient: _____

Child /Young Person to circle all they agree with:

Have you read (or had read to you) all of the information about this study?	Yes/No
Has somebody else explained this study to you?	Yes/No
Do you understand what this study is about?	Yes/No
Have you asked all the questions you want?	Yes/No
Have you had your questions answered in a way that you understand?	Yes/No
Do you understand it is OK to stop taking part at any time?	Yes/No
Is it alright to have some extra blood and spinal fluid samples taken?	Yes/No
Are you happy to take part in this study?	Yes/No
Are you happy to take part in future research?	Yes/No
Are you happy for us to use your MRI scan?	Yes/No

If any of your answers are 'no', you can discuss them now – but if you do not want to take part, do not sign your name!

If you do want to take part, you can write your name below

Your name: _____

Date: _____

The doctor who explained this clinical trial to you needs to sign too:

Print Name: _____

Sign: _____

Date: _____

Thank you for taking part.

Clinical trial number: _____

Centre Number: _____

Patient Study Number: _____

CONSENT FORM
(For Parents/Guardians)

Name of Patient**:** _____

	Please initial box
1. I confirm that I have read and understand the information sheet dated **22.10.2014 (version 1.4)** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my child's participation is voluntary and that I am free to withdraw my child from the study at any time without giving any reason, without their medical care or legal rights being affected.	
3. I understand that relevant sections of my child's medical notes and data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my child taking part in this research. I give permission for these individuals to have access to my child's records.	
4. I agree to routine blood and spinal fluid samples during my child's illness(es) and that the results of their MRI can be used for this study.	
5. I agree to blood and spinal fluid samples being taken during my child's illness(es), to be stored on behalf of the research team, by a licensed biobank for the possibility of future studies to be conducted.	
6. I agree to a DNA sample being taken during routine venepuncture and being stored on behalf of the research team, by a licensed biobank for the possibility of future studies to be conducted.	
7. I agree to my child's GP being informed of their participation in the study.	
8. I agree that I can be contacted in the future regarding future studies.	
9. I agree for the study team in London to keep details of my child's name and date of birth for future contact.	
10. **I understand that information held by the NHS and records maintained by The NHS Information Centre and the NHS Central Register may be used to help contact me and provide information about my child's health status.**	
11. I agree for my child to take part in the above study.	

_____	_____	_____
Name of Parent/ Guardian	*Date*	*Signature*
_____	_____	_____
Name of Person Taking Consent	*Date*	*Signature*

Patient Study Number: _____

Clinical trial number: _____

Centre Number: _____

Patient Study Number: _____

CONSENT FORM

Name of Patient**:** _____

	Please initial box
1. I confirm that I have read and understand the information sheet dated **22.10.2014 (version 1.4)** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving any reason, without my medical care or legal rights being affected.	
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
4. I agree to routine blood and spinal fluid samples during my illness(es) and that the results of my MRI can be used for this study.	
5. I agree to blood and spinal fluid samples being taken during my illness(es) to be stored on behalf of the research team, by a licensed biobank for the possibility of future studies to be conducted.	
6. I agree to a DNA sample to be taken during routine venepuncture and to be stored on behalf of the research team, by a licensed biobank for the possibility of future studies to be conducted.	
7. I agree to my GP being informed of my participation in the study.	
8. I agree that I can be contacted in the future regarding future studies.	
9. I agree for the study team in London to keep my details for future contact.	
10. I understand that information held by the NHS and records maintained by The NHS Information Centre and the NHS Central Register may be used to help contact me and provide information about my health status.	
11. I agree to take part in the above study.	

_____	_____	_____
Name of Patient (over 16)	*Date*	*Signature*

_____	_____	_____
Name of Person Taking Consent	*Date*	*Signature*

Patient Study Number: _____

Biological Samples Collection and Shipment to BioBank

Standard Operating Procedure

Contents

PURPOSE

The purpose of this protocol is to describe procedures for collecting and transporting specimens from STRIVE Trial participants to the appropriate BioBank (contact details page 5).

Wales Neuroscience Research Tissue Bank will receive samples from STRIVE trial centres in Birmingham, Bristol, Liverpool, Manchester and Wales.

The KCL Infectious Diseases BioBank will receive samples from the rest of the STRIVE trial centres.

The samples will be obtained from paediatric and adult patient populations presenting with symptoms of transverse myelitis.

SCOPE

This protocol is written for research personnel at NHS sites participating in STRIVE Trial.

RESPONSIBILITIES

Practitioners taking blood and CSF samples should be GCP trained and their involvement should be clearly recorded on the delegation log. They should have sufficient experience and training to perform these activities safely and at minimum patient discomfort according to local research governance procedures.

SAMPLES REQUIRED

Samples listed in the table below should be collected on the same day if possible. Morning collection will be required in order to allow sufficient time for delivery to the appropriate BioBank.

Tissue to collect	Volume*	Collection Tube	Collected at Baseline (T0)	Collected at 6 months follow up (T3)
Serum	10 ml	SST, allow to sit at least 30 min at room temp.	✓	✓
Plasma	10 ml	EDTA, gently invert to mix 8-10 times	✓	✓
DNA	10 ml	EDTA, gently invert to mix 8-10 times	✓	
PBMC**	10 ml	EDTA or sodium heparin, gently invert to mix 8-10 times	✓	
RNA	10 ml	PAX tube	✓	
CSF	12 ml	Sterile polypropylene tube with lid	✓	

NOTE**: These volumes may not be appropriate for **paediatric patients** but aim to collect as much as possible. ***Minimum volumes for each paediatric sample should be around ***50% of the adult volumes***.

****NOTE**: PBMC samples to be collected from patients who have never been treated with steroids, immune-modulatory or immune-suppressive medication. If there is prior history of treatment with any of the drugs in these categories PBMC samples can be collected if sufficient time has lapsed since the treatment:

- IV pulse steroids: 30 days
- systemic oral steroids: 30 days

- immunomodulatory agent (glatiramer acetate or interferon b): 3 months
- immunosuppressive agent (azathioprine/ methotrexate): 6 months
- biologic therapy: do not collect blood for PBMC

METHOD FOR BLOOD EXTRACTION

1. Prior to blood extraction ensure informed consent from patient and/or guardian according to STRIVE study protocol was obtained.

2. Explain the procedure to participant giving time for any questions and ensure the patient is comfortable with the procedure.

3. Ensure all equipment is ready to hand in a tray next to the participant. Blood sampling tray should contain:

- SST, EDTA, Sodium heparin and PAX collection tubes
- Syringe with a green/blue needle or Vacutainer system with butterfly needle attachment
- Cotton Swab/Gauze
- Alcohol Swab
- Tourniquet
- Plastic gloves

4. Follow local procedures for safe blood extraction and ensure that collection tubes are full.

5. Label the tubes with: patient's **STRIVE PIN number, date and time blood sample was taken.**

6. Complete **STRIVE sample collection form** (see Appendix) which will be couriered to the BioBank with the samples at ambient temperature.

7. **Send to the BioBank as soon as possible to be delivered before 2 pm.**

METHOD FOR CSF EXTRACTION

1. Prior to CSF extraction ensure informed consent from patient and/or guardian according to STRIVE study protocol was obtained.

2. Explain the procedure to participant giving time for any questions and ensure the patient is comfortable with the procedure.

3. Ensure that lumbar puncture tray is complete and ready for use. Usually it will contain:
   - Povidone-iodine (10%) (Betadine®) and/or isopropyl alcohol (70%) with applicators or sterile pads
   - Fenestrated drape
   - Local anesthetic (lidocaine 1%, (10mg/mL) 1-2 mL)
   - Syringe with small needle (1-2 inch, ~23g) for use with local anaesthetic
   - 3.5 inch lumbar puncture needle (22 gauge atraumatic recommended)
   - Sterile polypropylene tubes with caps for CSF collection

4. Position patient appropriately for procedure and follow locally approved standards for safe extraction of CSF. It is recommended that location for extraction is between L3/L4 or L4/L5.

5. Label the tubes with: patient's **STRIVE PIN number, date and time blood sample was taken.**

6. Complete **STRIVE sample collection form** (see Appendix) which will be couriered to the BioBank with the samples.

7. **Send to the BioBank as soon as possible to be delivered before 2 pm.**

In some instances it may not be possible to collect blood and CSF samples on the same day so collect them on two consecutive mornings and deliver each sample to the BioBank as soon as possible on the day of collection.

BIOBOTTLE AND SHIPPING INSTRUCTIONS

1. Place *clearly labelled* blood and CSF tubes (patient study number, date and time of sample collection) inside a plastic bag first, then into the Biobottle. Aim to send all samples from a patient to the BioBank together.
2. Ensure the absorbent material is in the Biobottle.
3. Ensure the correct sample collection forms are placed with the matched blood and CSF samples.
4. Please ensure that all contents are inside the package before closing.
5. Please ensure the outside of the shipment box is clearly labelled with sender's details (the name and address of the person responsible at site for sending the samples with a contact telephone number) as well as the address of the BioBank to which the samples need to be couriered.
6. After taking a sample, the research nurse (or designated site person) at the STRIVE trial centre will call the specialist medical couriers (CitySprint Couriers Tel: 0845 020 3000) to arrange collection and delivery to the appropriate BioBank.
7. Upon booking the courier, a reference number will be provided by CitySprint.
8. **For deliveries to the KCL Infectious Diseases BioBank** the reference number will be communicated via email (biobank@kcl.ac.uk) by the site's designated person.

   The courier will transport the sample to the Secretaries Office, Programme in Infection and Immunity, KCL, 2nd Floor Borough Wing, Guy's Hospital where the receiving individual will confirm receipt of the sample. The Secretaries' Office will ensure rapid sample transfer to BioBank staff who will then email the sender of the sample to confirm receipt of the sample.
9. **For deliveries to the Wales Neuroscience Research Tissue Bank** the reference number will be communicated via email (WNRTB@Cardiff.ac.uk) by the site's designated person. Additionally they can be phoned using telephone number 02920 743454.
10. In addition to the tracking number please quote **'STRIVE Trial'** when alerting the BioBanks that the samples have been collected from the site.
11. If the courier has not collected the samples within 90 minutes, the person who booked the courier should contact CitySprint to find out the status, quoting the reference number, and notify the appropriate BioBank of any delays.
12. If the BioBank staff have not confirmed receipt of the samples within two hours of collection from the trial centre by CitySprint, the courier will be contacted and the sample traced.

TIMING OF SAMPLE DELIVERY

After collection samples should be sent to the BioBank as soon as possible using CitySprint Couriers. Please ensure that the samples are ***not sent*** to the BioBank ***after 2 pm***, Monday to Friday.

Once samples are safely secured inside the Biobox and ready for transfer to BioBank, please phone or email the contacts at the BioBank of their impending arrival so arrangements can be made to store the samples.

NOTE: For samples collected at **6 months follow up**, please contact the relevant BioBank well ahead of time and give them the date when the samples will be sent to them for processing.

PERSONNEL

Members of clinical staff trained to take blood and/or CSF, including doctors and nurses on the unit.

HEALTH AND SAFETY

1. Standard precautions are required. Always wear gloves when handling blood samples.

2. Refer to the risk assessment, hazard data sheets and the Departmental policy at your site for additional safety information.

3. Please take all reasonable efforts to notify the BioBank of any extraneous agents, or biologically active contaminants that the sender is aware of (for example, but not limited to, HIV, hepatitis B, tuberculosis and transmissible spongiform encephalopathies) which may have been or are present in the samples.

BIOBANKS' CONTACT DETAILS

Sample Delivery Address	Lab Co-ordinator	Telephone	Email	Trial Sites
The KCL Infectious Diseases BioBank Secretaries Office Programme of Infection and Immunity Second Floor Borough Wing Guy's Hospital Great Maze Pond London SE1 9RT	Christine Mant John Cason	020 7188 3069 020 7188 1180	Biobank@kcl.ac.uk john.cason@kcl.ac.uk	London Liverpool Oxford Southampton Newcastle Nottingham
Wales Neuroscience Research Tissue Bank For the attention of Dr Sam Loveless Welsh Neuroscience Research Tissue Bank, C/O Reception Desk Henry Wellcome Building Cardiff University Heath Park Campus Cardiff CF14 4XN	Samantha Loveless	029 2074 3454	LovelessS1@cardiff.ac.uk	Birmingham Bristol Manchester Wales

APPENDIX: STRIVE TRIAL SAMPLE COLLECTION FORM

Please ensure that this form is sent to the BioBank with patient's samples but a copy should also be filed with patient's study notes.

Please send the samples to the BioBank as soon as possible after collection.

STRIVE TRIAL SAMPLE COLLECTION FORM

Name of the hospital.....

STRIVE Patient ID:.....

DOB:.....

Gender: Male ☐ Female ☐

Initials:.....

Date sample collected:.....

Time sample collected:.....

Patient did/did not *(please delete as appropriate)* receive steroid/immunomodulatory/suppressive treatments in the last 30 days/ 3 months/6 months.

Total Samples Collected:

TUBE	Quantity (ml)	Study time point	
		T0 (baseline)	T3 (6 M follow-up)
SST			
EDTA			
Sodium Heparin			
PAX tube			
Sterile polypropylene tube with lid			

1. PROTOCOL

1.1 Protocol Short Title/Acronym

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**

1.3 Sponsor

Name:	Guy's and St Thomas' NHS foundation Trust
Contact Person	Jackie Pullen
Address:	Guy's & St Thomas' NHS Foundation Trust 16th Floor, Guy's Tower, Guy's Hospital, Great Maze Pond, London SE1 9RT
Telephone:	020 7188 5732
Fax:	020 7188 8330
Email:	Jackie.Pullen@kcl.ac.uk

1.4 Chief Investigator

Name:	Dr Ming Lim (Consultant Paediatric Neurologist)
Address:	Children's Neurosciences, 1st Floor, D Block South Wing, St Thomas' Hospital, SE1 7EH
Telephone:	020 7188 4002
Fax:	020 7188 4269
Email:	Ming.Lim@gstt.nhs.uk

1.5 Name and address of Co-Investigator(s), Statistician, Laboratories etc

Name:	Dr Michael Absoud (Consultant and Research Fellow, Paediatric Neurodisability)
Position/ Role:	Co-Investigator, project co-ordinator and manager (Paediatrics)
Address:	Children's Neurosciences, 1st Floor, D Block South Wing, St Thomas' Hospital, SE1 7EH
Telephone:	020 7188 3995
Fax:	020 7188 4665
Email:	michael.absoud@gstt.nhs.uk

Name:	Dr Anu Jacob (Consultant Neurologist)
Position/ Role:	Co-investigator, project co-ordinator and manager (Adults)
Address:	The Walton Centre NHS Foundation Trust, Lower Lane, Fazakerley, Liverpool, L9 7LJ
Telephone:	0151 529 5420
Fax:	0151 529 5513
Email:	anu.jacob@thewaltoncentre.nhs.uk

Name:	Prof Gavin Giovannoni (Professor of Neurology)
Position/ Role:	Co-investigator, methodological input and clinical trial expertise
Address:	Centre for Neurosciences, Barts and The London School of Medicine and Dentistry, 4 Newark Street, London, E1 2AT
Email	g.giovannoni@qmul.ac.uk

Name:	Dr Jackie Palace (Consultant Neurologist)
Position/ Role:	Co-investigator, methodological input, clinical input and clinical trial expertise
Address:	Dept of Neurology, Neurosciences Offices, Level 3, West Wing, John Radcliffe Hospital, Oxford, OX3 9DU
Email:	jacqueline.palace@ndcn.ox.ac.uk

Name:	Prof Neil Robertson (Prof of Neurology)
Position/ Role:	Co-Investigator and Coordinator: Central Biobank
Address:	Institute of Psychological Medicine and Clinical Neurosciences, 2nd Floor, B-C Link Corridor, Cardiff University School of Medicine, UHW Main Building, Heath Park, Cardiff CF14 4XN
Telephone:	029 20 745 403, ext. 5403
Email:	RobertsonNP@cardiff.ac.uk

Name:	Dr Mike Pike (Consultant Paediatric Neurologist)
Position/ Role:	Co-Investigator and methodological input
Address:	John Radcliffe Hospital, Oxford
Email:	Mike.Pike@ouh.nhs.uk

Name:	Prof Paul McCrone (Professor of Health Economics)
Position/ Role:	Co-Investigator, Health economic analysis
Address:	Centre for the Economics of Mental and Physical Health, P024 Institute of Psychiatry, King's College London, Denmark Hill, London, SE5 8AF
Email:	paul.mccrone@kcl.ac.uk

Name:	Dr Peter Brex (Consultant Neurologist)
Position/ Role:	Co-Investigator, methodological input and clinical expertise
Address:	Department of Neurology, 9th floor, Ruskin Wing, Denmark Hill, King's College Hospital, London, SE5 9RS
Email	p.brex@nhs.net

Name:	Dr Olga Cirrarelli (Reader in Neurology)
Position/ Role:	Co-Investigator, methodological input and clinical expertise
Address:	UCL Institute of Neurology, Queen Square, London WC1N 3BG
Telephone:	020 3448 3419
Fax:	020 7813 6505
Email:	olga.cirrarelli@uclh.nhs.uk

Name:	Prof Andrew Pickles (Prof of Biostatistics)
Position/ Role:	Statistician & methodological input
Address:	Institute of Psychiatry, Box PO20, De Crespigny Park, London, SE5 8AF
Email:	andrew.pickles@kcl.ac.uk

Name:	Dr Jennifer Hellier (Statistician)
Position/ Role:	Primary Statistician & methodological input
Address:	Department of Biostatistics, Institute of Psychiatry, Box PO20, De Crespigny Park, London, SE5 8AF
Telephone:	0207 848 0323
Email:	jennifer.hellier@kcl.ac.uk

Name:	Ms Caroline Murphy
Position/ Role:	Co-Investigator/ Operational Director, KCTU
Address:	King's Clinical Trials Unit, King's College London, PO64, M2.06, Institute of Psychiatry, London, SE5 8AF
Telephone:	0207 848 5273
Fax:	0207 848 5229
Email:	caroline.murphy@kcl.ac.uk

Name:	Ms Joanna Kelly
Position/ Role:	Co-investigator/ Data Management Strategic Lead
Address:	King's Clinical Trials Unit, King's College London, PO64, M2.06, Institute of Psychiatry, London, SE5 8AF
Telephone:	0207 848 5273
Fax:	0207 848 5229
Email:	joanna.kelly@kcl.ac.uk

Name:	Mrs Rosemary Howe
Position/ Role:	Clinical Trial Manager
Address:	9th Floor, Capital House, Guy's Campus, 42 Weston Street, London SE1 3QD

Telephone:	020 7848 6245
Fax:	TBC
Email:	TBC

Name:	Dr Andrea Wartenberg
Position/ Role:	Vice President Corporate Clinical Research
Address:	Biotest AG Landsteinerstraße 5 D-63303 Dreieich Germany
Fax:	0049 6103/801-341
Telephone:	0049 6103/801-497

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 NHS Foundation Trust - Barts Health NHS Trust
Liverpool	05	06	- Alder Hey Children's NHS Foundation Trust - 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 NHS Trust, Wales
Bristol	13	14	- North Bristol NHS Trust - University Hospital Bristol NHS Trust
Manchester	15	16	-Central Manchester University Hospitals NHS Foundation Trust - Royal Salford NHS Foundation Trust
Southampton	17	18	University Southampton NHS Trust
Newcastle	19	20	Newcastle Hospitals NHS Foundation Trust
Nottingham	21	22	Nottingham University Hospitals NHS Trust
Edinburgh		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:	Guys 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) ▪ Lack 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 (Wingerchuck 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 divided doses over 5 days (or given over 2 days 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:	draft v2.3 09/01/2015
Version And Date Of Protocol Amendments:	V2.0 30/09/2014 V2.1 15/10/2014

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	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, 2014). 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, 2012), 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 1988). 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 a 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 ≥13at 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 (variations of 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 divided doses over 5 days
- 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 divided doses over 2 days

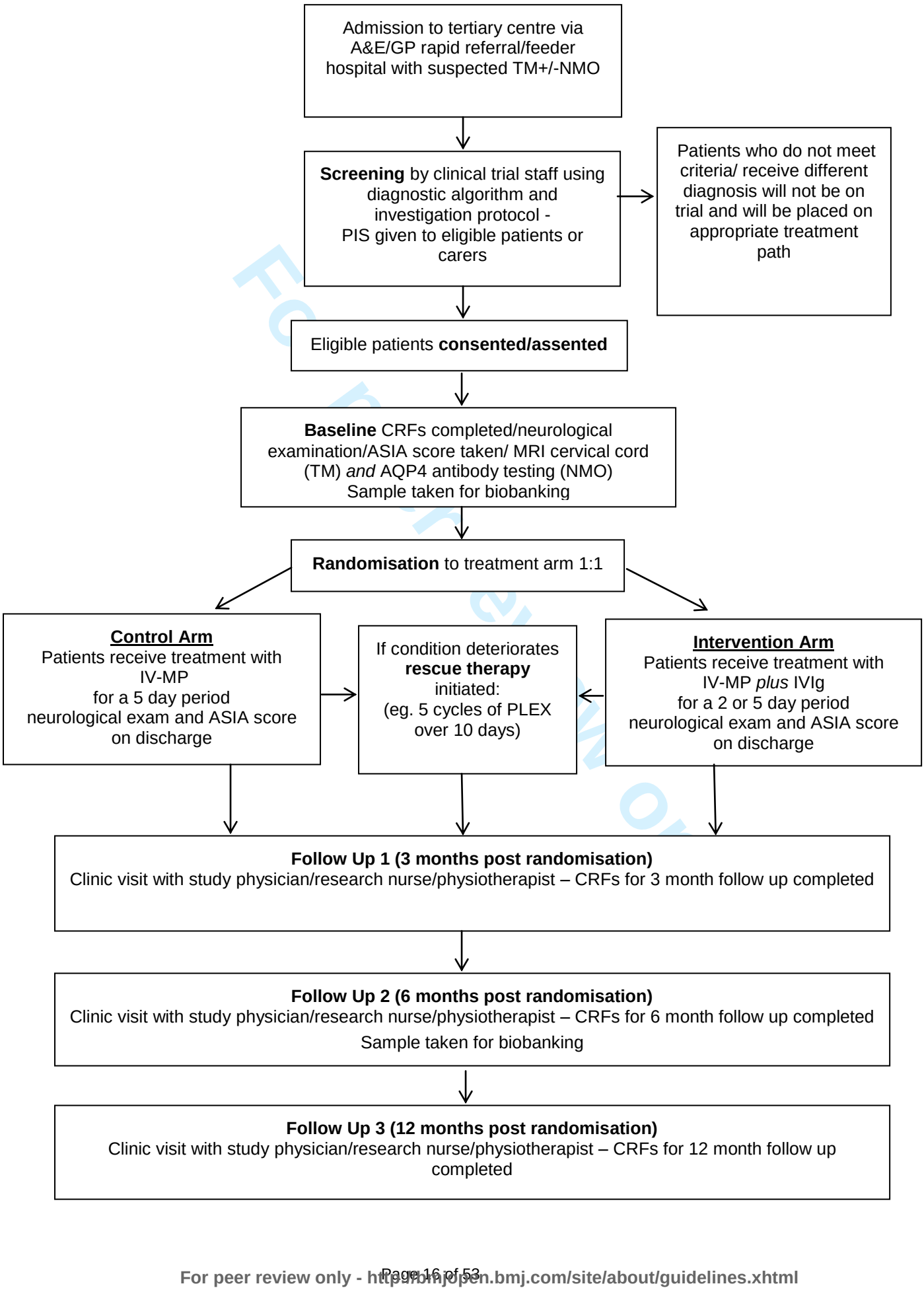
Patients may be recruited and randomised up to 5 days from the date of first commencing steroid therapy or up to 21 days from the onset of symptoms (if definitely known)..

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 secured 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 coordinator. 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 practice 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 with PLEX will be instituted, in accordance with local guidelines (please see section 6.5 above). 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 (Wingerchuck 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 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

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 11 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 Patient Registration

After consent has been signed, the patient will be registered on the MACRO system, which can be accessed online by a trained member of trial staff who has been allocated a username and password (via trial manager). The system is accessed at **www.ctu.co.uk** by clicking **'MACRO EDC v4'** in the **Useful Links** box on the lower right hand side of the page. Following entry of registration details the system will generate a unique patient identification number (PIN) which will be used, with patient initials, for that patient throughout the study on all CRFs and eCRFs, and will be the only method of identification (for information on the MACRO system (see section 20). The PIN will be a five digit number, the initial two digits corresponding to the centre the patient was recruited from.

8.5 Randomisation Procedure

Patients will be randomised to treatment arms via an online system based at King's Clinical Trials Unit (KCTU). The system can be accessed at **www.ctu.co.uk** by clicking **'randomisation – advanced'**. This system can only be accessed by trained trial staff that have previously been allocated a username and

password. Requests for passwords are via the Trial Manager to the King's CTU. Details of individuals responsible for patient randomisation will be kept on local delegation of duties log.

Please make sure that baseline data has been collected for the patient just prior to randomisation (see section 9 for further details).

Also note that randomisation system is *not* linked to the MACRO (main study) database (see section 20).

Allocation to trial arms will be at the level of the individual patient, using stratified block randomisation. The block will randomly vary in length of 2 and 4, and patients will be stratified by service type (adult or child). The randomisation system will automatically generate emails at the point of randomisation which will be sent to appropriate members of the study team. The trial manager and those administering treatment are unblinded and will be informed of the allocated treatment arm. Those who will carry out follow up assessments will be blinded, therefore they will just receive notification of randomisation in order to start scheduling appointments. A study specific prescription will be completed and sent to pharmacy for dispensing. Any problems with the online randomisation system should be reported to the trial manager or to the King's CTU at CTU@kcl.ac.uk / 0207 848 0532.

8.6 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 (ie. 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.

8.7 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

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 with following data items:

Date of Admission, Patient ID (NHS or Hospital number), Patient DOB, Suspect TM (yes/no), Eligible for the study (yes/no), Consented to take part (yes/no), Reason for not being included in the study, Date randomised, Study ID, Date 3 months follow up, Date 6 months follow up, Date 12 months follow up, Any comments. An excel spreadsheet template for a screening log will be sent to each trial centre by the Trial Manager.

If patients/ guardians consent to take part in the study please ensure that randomisation takes place as soon as possible but IVIg treatment has to be immediately available for patients randomised to treatment group.

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, we envisage that a proportion of patients will receive IVIg with IV MP on at least one day as shown in this table:

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	TD2	TD 3	TD 4	TD 5
IV MP (Control arm)	◄- - - - - - - - - - - - - - X - - - - - - - - - - - - - - ► (A total of 5 days treatment, which can commence on day of admission. Patients may be recruited up to 5 days from the date of commencing IV MP (D1))								
IV MP (Intervention arm)	◄- - - - - - - - - - - - - - X - - - - - - - - - - - - - - ► (A total of 5 days treatment, which can commence on day of admission. 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**			

If patient's symptoms worsen during treatment or there is no improvement at the end of treatment the patient will have prolonged hospitalisation and rescue therapy should be applied (as shown in table below):

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.

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 also to **Appendix 3** for additional details of study procedures.

ASIA IMPAIRMENT SCORE (AIS) is the main eligibility criterion as well as the primary outcome. It should be obtained immediately before randomisation as baseline measure, even if it was recorded during screening or any earlier time point prior to randomisation.

If the patient deteriorates and needs to have rescue therapy please evaluate ASIA motor, sensory and impairment scores before the rescue therapy is initiated.

Each assessor needs to have training and obtain certification for ASIA Sensory and Motor Scoring evaluation (see: http://lms3.learnshare.com/home.aspx). Please forward copies of the certificates to the STRIVE Trial Manager.

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.

Schedule Table:

Schedule Treatment day (D) Timepoint (T)	**T0** (Screening, baseline and prediagnosis tests)	**T1** (Treatment and discharge)							**T2** 3M	**T3** 6M	**T4** 12M	Withdrawal
		TD 1‡	TD 2	TD 3	TD 4	TD 5	*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	x								x	S	x	
≥13 yrs EQ-5D-5L	x								x	S	x	
≥13 yrs SCI QoL Basic dataset									x	S	x	
CSRI									x	S	x	
≥13 yrs SCI Bladder										T	x	
≥13 yrs SCI Bowel										T	x	
5-7yrs Peds QL										T	x	

2-4 yrs Peds QL										**T**	**x**	
Treatment form						**x**						
Concomitant medications								**x**	**x**	**x**	**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**	**x**	**x**	**x**	**x**						
Study Status Form									**x**	**x**	**x**	
*Withdrawal form (at any time point)												**x**

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

‡ IVIg Treatment Day1 (TD1) = shown in this table separately but the first day of IVIg treatment should happen on the same day as day of randomisation

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

9.2 By Visit

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

Screening and baseline assessments will be made in the tertiary centres by a study physician/research nurse, and as treatment has not yet been allocated, blinding will not be of issue.

Post randomisation, all assessments and study data taken during the hospital stay, and all follow up assessments 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.

9.3 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. 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 (http://content.learnshare.com/courses/120/440012/story.html).

During the trial, the Kurtzke Neurological exam (Neurostatus score) and the SCI scales for Bladder, Bowel and Pain will also be used. Any members of study team who do not routinely use these exams/scales will also need to undergo training from the PI. All training must be recorded in the Staff Training Log in the site Master Files.

9.4 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. 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 SOP will be provided to all investigators.

9.5 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 on MRI sequences, but wherever possible, gadolinium enhancement should be requested. Reports should 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

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

All assessments will be carried out by a physician/research nurse/physiotherapist blinded to treatment and will be reported using the appropriate assessment tools and questionnaires.

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:

Go to www.ctu.co.uk and click the link to MACRO EDC V4 on the lower right hand side of the screen.

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 2 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). Biotest AG will provide the study drugs.

24. Signatures

_____ _____

Chief Investigator Date

Print name

_____ _____

Statistician (if applicable) Date

Print name

25. References

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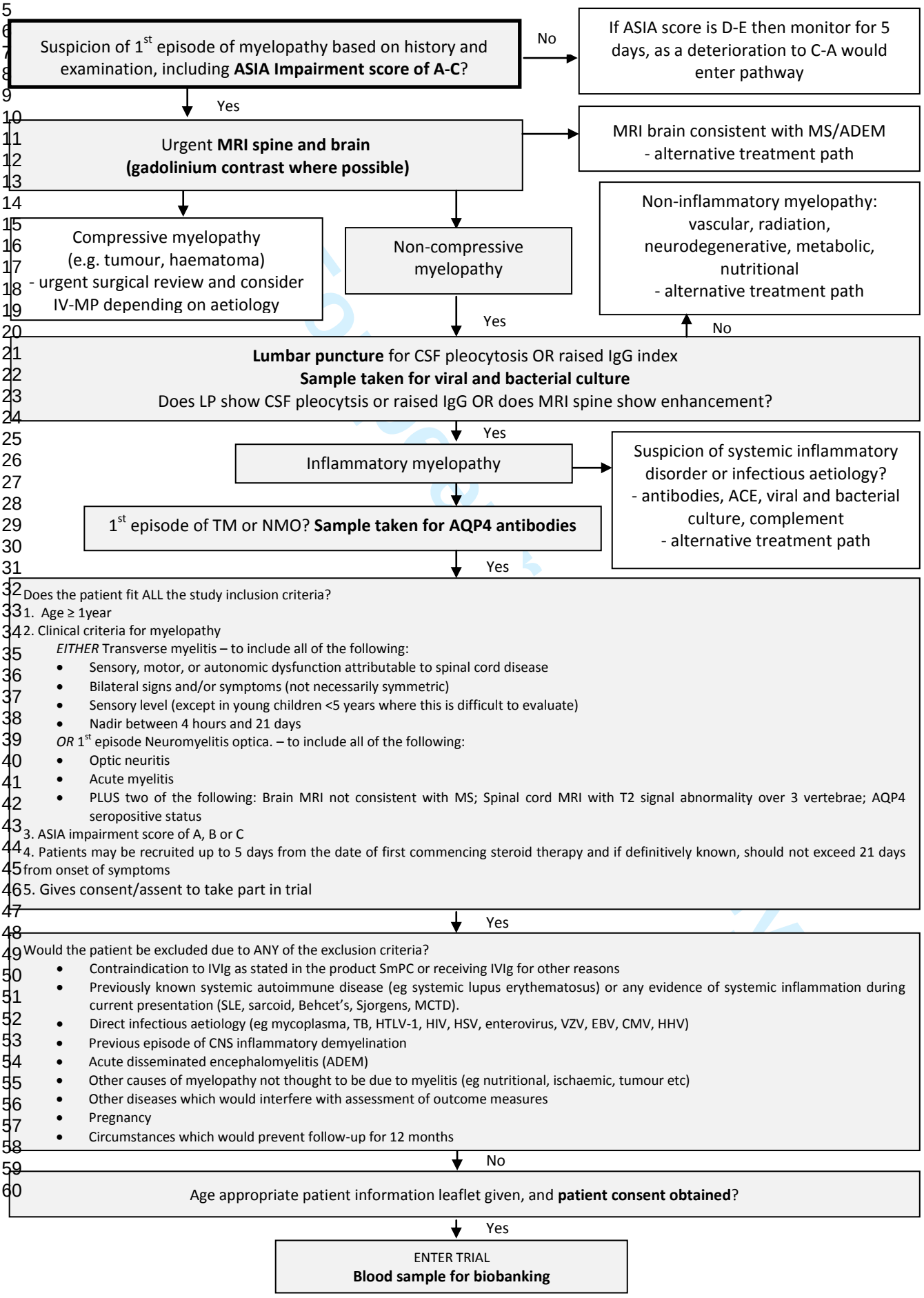
26. Appendices

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

Appendix 2: Clinico-radiological Diagnostic Algorithm



Appendix 3: Trial Procedures by Visit

IMPORTANT: All staff conducting ASIA, SCI and Kurtzke's functional and EDSS assessments MUST undergo training which has to be documented in the Site Training Log.

INITIAL CONTACT

Screening

A screening log will be kept at all sites (see section 9).

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
- ASIA Motor and Sensory (if patient ≥ 5 years of age) Scores including AIS (ASIA Impairment score of A, B or C is necessary for eligibility*)
- 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

* 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 recruited and 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.

Consent

If the patient meets all of the eligibility criteria, the clinician 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 patents 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.

- Equipment/Forms required:
- Patient Information Sheets (PIS) - child/adolescent/adult/parent
- Consent/Assent forms - child/adolescent/adult

After consent, study data can officially be collected:

- ASIA Sensory and Motor scores including AIS
- Results of pre-diagnosis tests form can be submitted as study data (including AQP4 and culture results when available).

Registration and Pre-Treatment (baseline) Assessment

As soon as consent has been obtained the patient should be **registered** on STRIVE trial database. The database is accessible at the following URL. 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. This number together with patient's initials and DOB will be required by STRIVE Randomisation database (see below). 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, 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 Syste,s and EDSS form)
- ASIA Motor, Sensory and Impairment Score fom

- Biobank Sample form

Randomisation = study time point T0

The patient will be randomised via the King's CTU online randomisation service (URL: 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, IV-Ig 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 and the score just prior to randomisation has to be recorded in the database.Forms required for randomisation:

Randomisation form

Following randomisation, all examinations and assessments should be performed by staff blinded to treatment.

Treatment = T1

The total study treatment period will be 5 days (see Section 9.1 for summary table) but if there are delays between admission and randomisation it can be extended up to 9 days overall.

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

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). 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
- Rescue Therapy form

Completion of Treatment/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
- Neurostatus Examination (Kurtzke Neurological and EDSS) form
- Rescue Therapy form (if required)
- Relapse form (if required)
- Withdrawal form (if required)

FOLLOW UP VISITS

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)
- Neurostatus scoring (Kurtzke's functional systems and EDSS)
- EQ-5D-Y (for patients aged 7-12 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 (separate form in the database)

Secondary endpoint:

ASIA Motor and Sensory scales components

Neurostatus exam (Kurtzke's functional systems and EDSS)

EQ-5D-Y (for patients aged 7-12.99 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 endpoint:

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

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 (separate form in the database)

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 7-12.99 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.

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/

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

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

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

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 $\bar{p} = \frac{1}{2}(p_C + p_E)$.

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

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

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.

APPENDIX 6: Professional Advert

Insert local logos

STRIVE

Insert local logos

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