

CLINICAL STUDY REPORT

Clinical trial identification

Title: A multicentre randomised controlled Trial of Intravenous immunoglobulin (IVIg) versus standard therapy for the treatment of transverse myelitis in adults and children

Acronym: STRIVE

Protocol number: PROTOCOL v5.0 27/11/2015

Study initiation date: 31/07/2015

Study completion date: 11/05/2016

Date of early termination: 11/05/2016

Date of report: 19/10/2016

Identifiers

IRAS number: 157664

EudraCT Number: 2014-002335-34

ISRCTN Number: ISRCTN12127581

REC Number: 14/SC/1329

ClinicalTrials.gov Number: NCT02398994

Funders Number: 11/129/148

Sponsor details

Name: Guy's and St Thomas' NHS foundation Trust

Contact Person: Dr Ming Lim

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Good Clinical Practice compliance

This study was performed in accordance with the GCP guidelines, as well as all applicable regulatory requirements. Monitoring of the trial ensured compliance with GCP

Objectives of trial

Primary objective:

The primary objective of the study was to evaluate if additional and early treatment with IVIG is of extra benefit in transverse myelitis compared to standard therapy of intravenous steroids.

Secondary objective:

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 and;
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

The STRIVE study was a multicentre, single-blind, parallel-group randomised controlled trial of IVIG versus standard therapy for treatment of Transverse myelitis (TM) in adults and children.

Scientific background

TM is a rare inflammatory disorder of the spinal cord affecting approximately 350 children and adults annually in the UK. TM attacks usually develop over 24 hours and in some cases can progress rapidly to a potentially devastating and sometimes life threatening condition. 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). NMO is a relapsing subset of TM, usually caused by antibodies to aquaporin-4. Clinically, patients have recurrent episodes of predominantly 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. 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. Given the disease severity and poor outcomes, plasma exchange (PLEX) has been used in addition to standard therapy with some effect. 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. Randomised controlled trials have demonstrated IVIG efficacy in a number of neurological conditions. In steroid-unresponsive CNS demyelination, IVIG is often used, although supporting data is limited to small case series and single case reports. IVIG appears to inhibit complement binding, neutralise pathogenic cytokines, down regulate antibody production, enhance remyelination and modulate phagocytosis and T-cell function. The majority of these factors are common across inflammatory disorders of the CNS including TM, providing a

strong rationale for its use. The availability, ease of administration, familiarity and safety also makes IVIG an attractive option in the acute setting

Ethics

Independent Ethics Committee

All versions of the protocol used, including amendments were reviewed and approved by an independent ethics committee. See appendix

Ethical Conduct of Study

The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki

Patient Information and Consent

Patients were consented following their review of the patient information sheet and screening by clinical trial staff. Clinical trial staff screened patients using diagnostic algorithm and investigation protocol. The Patient information sheet was given to eligible patients and carers, after which patients were consented.

Investigators and Study Administrative Structure

The administrative structure of the study is as described in the table below.

Chief Investigator	Hospital	Trusts
Ming Lim	Evelina Children's Hospital	Guy's and St Thomas' NHS Foundation Trust
Principal Investigators	Hospital	Trusts
Victoria Williams	St Thomas's Hospital	Guy's and St Thomas' NHS Foundation Trust
Cheryl Hemingway	Great Ormond Street	Great Ormond Street Hospital for Children NHS Foundation Trust
Rachel Kneen	Alder Hey Children's Hospital	Alder Hey Children's NHS Foundation Trust
Anu Jacob	The Walton Centre	The Walton Centre NHS Foundation Trust
Jackie Palace	John Radcliffe Hospital	Oxford University Hospitals NHS Trust
Evangeline Wassmer	Birmingham Children's Hospital	Birmingham Children's Hospital NHS Foundation Trust
Saiju Jacob	Queen Elizabeth Hospital	University Hospitals Birmingham NHS Trust
Neil Robertson	University Hospital of Wales	Cardiff & Vale University Health Board
Kayal Vijayakumar	Bristol Royal Hospital for Children	University Hospital Bristol NHS Foundation Trust
Siobhan West	Royal Manchester Children's Hospital	Central Manchester University Hospitals NHS Foundation Trust

Chief Investigator	Hospital	Trusts
Ming Lim	Evelina Children's Hospital	Guy's and St Thomas' NHS Foundation Trust
Principal Investigators	Hospital	Trusts
Katharine Forrest	Southampton General Hospital	University Hospital Southampton NHS Trust
Martin Duddy	Royal Victoria Infirmary	The Newcastle Hospitals NHS Foundation Trust
Katy Murray	Western General Hospital	NHS Lothian
Peter Brex	King's College Hospital	King's College Hospital NHS Foundation Trust

Trial Steering Committee	
Honorary chair	Prof Richard Hughes
Members	Ming Lim Anu Jacobs
Independent members	Claire Lundy (Paediatric Neurologist) Barbara Babcock (TM Society) Lew Gray (TM Society) Martin Kappler (Statistician) Mark Sanders (Clinician)

Data Monitoring Committee	
Honorary chair	Prof John Zajicek
Independent members	Sarah Cotterill (Statistician) Alasdair Parker (Clinician)

Trial Statisticians: Prof Andrew Pickles, Jennifer Helier and Rachel Holland

Clinical trial (IMP) supplier: Biotest Pharma GmbH

Date first patient enrolled: 31/07/2015

Date of last patient final visit: 11/05/2016

Population of Subjects

Number of subjects planned: 170 (85 per arm)

Number of subjects screened: 28

Number of randomised subjects: 2

Number of subjects withdrawn: 2

Principal criteria for inclusion:

Patients were eligible for inclusion into the trial if on presentation they:

1. Were aged 1 year or over
2. 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:
 - a. Sensory, motor, or autonomic dysfunction attributable to spinal cord disease
 - b. Bilateral signs and/or symptoms (not necessarily symmetric)
 - c. Sensory level (except in young children <5 years where this is difficult to evaluate)
 - d. Lack of MRI brain criteria consistent with MS (McDonald 2010 space criteria)
 - e. 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).

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
3. Have an ASIA Impairment score of A, B or C
 4. Give assent/consent to participate in the trial

Principal criteria for exclusion

Patients were excluded if they showed evidence of:

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. Pregnancy
8. Circumstances which would prevent follow-up for 12 months

Investigational medical product used: Intravenous Immunoglobulin (Intratect®)

Randomisation

Participants were randomised 1:1 to treatment with IV methylprednisolone alone (control arm) or IV methylprednisolone plus 2kg/kg IVIG in divided doses (treatment arm).

Blinding

Due to the technical challenges of masking IVIG from saline, the need for rapid recruitment and the fact that follow-up will be many months after the event using objective well-defined clinical endpoints; treatment will not be blinded (no placebo). The trial manager, pharmacy, and those administering treatment are not blinded; whilst staff carrying out primary outcome assessments at follow-up and statistical analyses will be blinded to intervention. Screening, baseline and discharge assessments were carried out in the tertiary centres by a study physician/research nurse. Following discharge from treatment in hospital, all primary outcome assessments at follow up in clinic at the tertiary centre or appropriate neurology centre, were carried out by a study physician/research nurse/physiotherapist who had been blinded to treatment. For consistency, wherever possible, the same blinded assessor was required to out the assessments at each time point. Although not mandatory secondary and tertiary outcome assessments were to be performed by a blinded member of staff at follow-up wherever possible.

Concomitant medication

Concomitant therapy (only relevant immune-modulatory medications) were recorded throughout the study on a Concomitant Medications Form. 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. As such, after administration of this product, it was recommended that 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 were advised to have their antibody status checked. Additionally, following immunoglobulin injection, 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).

Treatment compliance

Treatment with IMP was administered under supervision of the clinical trial staff, therefore full compliance with treatment was achieved.

Summary of results

The study was terminated early, due to a lower than expected rate of recruitment. Consequently, the trial failed to achieve its key objectives in determining if additional and early treatment with IVIG is of extra benefit in transverse myelitis compared to standard therapy of intravenous steroids.

Two patients were randomised into the study, both of whom were withdrawn from the study 6-month post randomisation. One participant, randomised into the control arm of the study, was a white female child, aged between 10 and 15, a student with unknown BMI. This participant had an ASIA impairment score of C prior to randomisation, meaning that motor function is preserved below the neurological level and more than half the key muscles below this level have muscle grade less than 3. At 3-months post randomisation this participant had improved to ASIA impairment score of D meaning that at least half of the key muscle functions below the neurological level have a muscle grade of 3 or above. The other participant, randomised into the intervention arm of the study, was a white adult male, aged between 60 and 65, in full-time employment with a BMI of 30. This participant had an ASIA impairment score of A prior to randomisation, meaning that no motor or sensory function is preserved in sacral segments S4 to S5. At 3 months post randomisation, this participant had not improved. Neither participant suffered a relapse during the trial.

Study end points

1. End point as per study design

a. Primary endpoint measure

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

b. Secondary endpoint measures

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

c. Tertiary endpoint measures

- i. International SCI Bladder/Bowel Data Set for patients aged ≥ 13 years at presentation to be completed at 6 and 12-months post randomisation

- ii. Children 2-4 years of age at presentation: Paediatric Quality of Life Inventory™ (PedsQL Parent Report for Toddlers) at 6 and 12 months
- iii. Children 5-7 years of age at presentation: Paediatric Quality of Life Inventory™ (PedsQL Parent Report for Young Children) at 6 and 12 months
- iv. Individuals \geq 13 years of age at presentation: International SCI Pain Basic Data Set at 6 and 12 months

2. Actual study end-point

The study was ended prematurely after almost a year of recruitment (measured from date of opening of first recruitment site). The two patients randomised into the study were withdrawn from the study following their 6-month visit post randomisation. As only two patients were randomised into the study, no statistical analysis will be carried out on the data from both patients.

There were no deviations related to study inclusion or exclusion criteria.

Adverse events

The adult participant suffered from two adverse events during the trial, a chest infection and pressure sores, which were not related to the trial and the paediatric participant suffered no adverse events.

Appendix

1. Independent Ethics Committee

National Research Ethics Service (NRES) Committee South Central – Berkshire B

Chair: Dr John Sheridan

2. Sample patient consent form

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 becomes 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) and others will receive both IV-MP and IVIg.

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 you 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. If blood and spinal fluid samples have already been taken, we would ask to store any leftover material if this is available.

Assessments

The doctor will perform some physical assessments and tests on you, mainly tests that all patients with TM undergo as recommended by the TM Consortium Working Group 2002. Further details of these assessments can be provided by the doctor.

Clinical Data and Questionnaires

The doctor will collect information about your normal health, family history, and your 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. In some cases the MRI scan needs to be examined more closely. In these cases, all personal information is removed from the scan and it will be sent to the imaging lead for STRIVE, Prof Olga Ciccarelli, UCL Institute of Neurology, Queen Square, London WC1N 3BG.

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 put in a biobank. 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.
- If you have already had samples taken, and do not need any further samples for your routine care, we will check with the lab if there is any leftover material we could send to the biobank.
- 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. 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 you 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 your 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 short-term 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, treatment with plasma exchange (PLEX) will be considered as an additional therapy. PLEX involves replacing the plasma in a person's blood. The possible use of an additional 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 and NMO 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 <TRUST NAME> Patient Advisory Liaison Service (PALS) on <INSERT LOCAL PALS NUMBER>, address: PALS, <INSERT LOCAL PALS ADDRESS>. This study is indemnified by Guy's & St Thomas' NHS Foundation Trust under the Clinical Negligence Scheme for Trusts.

All professional staff involved in the study hold professional indemnity to work within <TRUST NAME>. 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.

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 for the STRIVE study. However, if you agree, a sample of your DNA may be collected and stored for future research.

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 at 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 funded by the National Institute for Health Research Health Technology Assessment Programme (11/129/148) 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> or you can look at the study website:

www.guysandstthomas.nhs.uk/STRIVE

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 parents/guardians



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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.

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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 you 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. If blood and spinal fluid samples have already been taken, we would ask to store any leftover material if this is available.

Assessments

The doctor will perform some physical assessments and tests on your child, mainly tests that all patients with TM undergo as recommended by the TM Consortium Working Group 2002. Further details of these assessments can be provided by the doctor.

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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. In some cases the MRI scan needs to be examined more closely. In these cases, all personal information is removed from the scan and it will be sent to the imaging lead for STRIVE, Prof Olga Ciccarelli, UCL Institute of Neurology, Queen Square, London WC1N 3BG.

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.
- If your child has already had samples taken, and do not need any further samples for their routine care, we will check with the lab if there is any leftover material we could send to the biobank.
- 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. 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 short-term 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, treatment with plasma exchange (PLEX) may be considered as an additional therapy. PLEX involves replacing the plasma in a person's blood. The possible use of an additional therapy has been built into the 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 and NMO 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 <TRUST NAME> Patient Advisory Liaison Service (PALS) on <INSERT LOCAL PALS NUMBER>, address: PALS, <INSERT LOCAL PALS ADDRESS>. This study is indemnified by Guy's & St Thomas' NHS Foundation Trust under the Clinical Negligence Scheme for Trusts.

All professional staff involved in the study hold professional indemnity to work within <TRUST NAME>. 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.

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 for the STRIVE study. However, if you agree, a sample of your child's DNA may be collected and stored for future research.

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 funded by the National Institute for Health Research Health Technology Assessment Programme (11/129/148) 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> or you can look at the study website:

www.guysandstthomas.nhs.uk/STRIVE

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

Patient Information Sheet for Children Aged 6-11



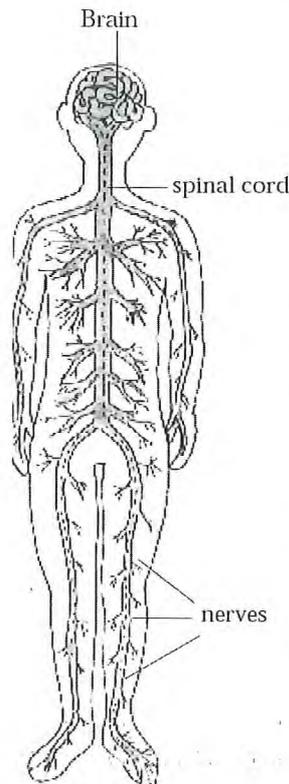
A study of the best treatment for transverse myelitis (TM)

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 spinal cord and 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. If you have already had samples taken we will check with the lab if there is any leftover material we could use. 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 and NMO 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 intravenous 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 like TM and NMO 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 you 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. If blood and spinal fluid samples have already been taken, we would ask to store any leftover material if this is available.

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 spinal cord and 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 and 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, treatment with plasma exchange (PLEX) will be considered as an additional 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 and NMO 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 Health Technology Assessment Programme (11/129/148) 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.guysandstthomas.nhs.uk/STRIVE or phone us on <Insert the number of local study contact>.

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.

**PRINCIPAL OR COORDINATING
INVESTIGATOR(S) SIGNATURE(S)**

STUDY TITLE: A multicentre randomised controlled Trial of Intravenous immunoglobulin (IVIg) versus standard therapy for the treatment of transverse myelitis in adults and children.

STUDY AUTHOR(S):

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

CHIEF INVESTIGATOR: Dr Ming Lim

SIGNATURE(S)



AFFILIATION: Children's Neurosciences, 1st Floor, D Block South Wing, St Thomas' Hospital, London. SE1 7EH

DATE: 19/10/2016