

TREAT-NMD/ JTSMA UK National SMA Registry PROTOCOL

1.0 INTRODUCTION

TREAT-NMD is a European Union funded Network of Excellence and was launched on 1st January 2007. The network brings together 21 partner organisations throughout 11 European countries enabling experts to work together to encourage harmonisation and reduce fragmentation in the neuromuscular community accelerating clinical trials and promoting common Standards of Care.

The Jennifer Trust for Spinal Muscular Atrophy is a UK national charity dedicated to supporting people affected by SMA and investing in essential research into causes, treatments and eventually a cure for the condition.

The UK national SMA registry is a joint venture between TREAT-NMD and The Jennifer Trust with the aim of encouraging UK SMA patients to register so that they may be considered for relevant clinical trials, receive the most up to date information regarding standards of care for their disease and help provide the research community with an understanding of SMA prevalence. Data from patients who register on the UK National SMA Registry will also be included in the European TREAT-NMD registry along with other patient data from across Europe.

Spinal Muscular Atrophy (SMA) is a term applied to a number of different genetic disorders which manifest themselves in muscle weakness due to loss of motor neurons in the spinal cord and brainstem.

SMA is an autosomal recessive disorder therefore all forms of SMA are caused by inheritance of a mutated gene from each parent. If both parents are carriers each infant has a 25% chance of developing the illness. All forms of SMA have a combined incidence of about 1 in 6,000. SMA is the most common cause of genetically determined neonatal death with the gene frequency being around 1:80.

The most common form of SMA is caused by mutation of the SMN gene, which manifests itself over a wide severity range affecting infants through to adults. This spectrum has been divided into four groups by the level of weakness.

- **Infantile SMA - Type 1 or Werdnig-Hoffmann disease** (onset generally 0-6 months). SMA type 1 is the most severe and manifests in the first year of life with the inability to ever maintain an independent sitting position.
- **Intermediate SMA - Type 2** (onset generally 7-18 months). Type 2 SMA describes those children who are unable to stand and walk, but who are able to maintain a sitting position at least some time in their life.
- **Juvenile SMA - Type 3 or Kugelberg-Welander disease** (onset generally >18 months). SMA type 3 describes those who are able to walk at some time

and symptoms include abnormal gait, fine tremor of the fingers, difficulty running, climbing steps and rising from a chair. However many of these children may appear "normal" until they are five or even older.

- **Adult SMA - Type 4.** Weakness usually begins in late adolescence in tongue, hands, or feet then progresses to other areas of the body. Course of disease is much slower and has little or no impact on life expectancy.

Other forms of SMA are caused by mutation of other genes some are known but others are yet to be identified. Some of the known forms include Hereditary Bulbo-Spinal SMA or Kennedy's disease, Spinal Muscular Atrophy with Respiratory Distress (SMARD 1) and Distal SMA with upper limb predominance.

The course of SMA is directly related to the severity of weakness. Infants with the severe form of SMA frequently succumb to respiratory disease due to weakness of the muscles that support breathing. Children with milder forms of SMA naturally live much longer although they may need extensive medical support, especially those at the more severe end of the spectrum.

Although gene replacement strategies are being tested in animals, current treatment for SMA consists of prevention and management of the secondary effect of chronic motor unit loss. It is likely that gene replacement for SMA will require many more years of investigation before it can be applied to humans. Due to molecular biology, there is a better understanding of SMA. The disease is caused by deficiency of SMN (survival motor neuron) protein, and therefore approaches to developing treatment include searching for drugs that increase SMN levels, enhance residual SMN function, or compensate for its loss.

Much can be done for SMA patients in terms of medical and, in particular respiratory, nutritional and rehabilitation care. However, there is currently no drug known to alter the course of SMA. Significant progress has been made in pre-clinical research towards an effective treatment. Several drugs have been identified in laboratory experiments that hold promise for patients. To evaluate if these drugs benefit SMA patients clinical trials are needed and this is where the SMA registry can help- by facilitating and accelerating clinical trials.

Several drugs are currently under clinical investigation for the treatment of SMA - these include Butyrates, Valproic acid, Hydroxyurea and Riluzole. Further drugs are also in early stage development (eg TRO 19622).

The overall goal of the TREAT-NMD project is to find new ways of treating patients with diseases such as Spinal Muscular Atrophy. Although there is still no cure for these inherited neuromuscular diseases, major progress has been made in recent years towards new therapeutic strategies. Several of these strategies target specific genetic defects, some of which are so rare that only a few patients in Europe will have the right profile for a particular clinical trial. The aim of the patient registry is therefore to make sure that these patients can be found and invited to take part in clinical trials quickly and efficiently. Data collated in the

registries will also help researchers answer other important questions about how common SMA is in countries across Europe, and will be a useful way of ensuring that patients can be kept informed about the latest information that might be relevant to their disease.

2.0 OBJECTIVES

The primary objectives of the SMA registry are to:

- Accelerate and facilitate clinical trials by locating potential research subjects quickly and efficiently.
- Facilitate in the planning of clinical trials.
- Assist the neuromuscular community with the development of recommendations and standards of care.
- Characterise and describe the SMA population as a whole, enhancing the understanding of SMA prevalence across Europe.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

All patients with a confirmed SMA diagnosis (or pending diagnosis) are eligible for inclusion. Diagnosis will be confirmed via genetic testing results.

3.2 Exclusion Criteria

There are no exclusion criteria for this registry.

4.0 THE REGISTRY PROGRAMME

4.1 Design

The SMA Registry is a UK national registry for patients with SMA; no experimental intervention is involved. Patients will receive information on the most up to date standards of care relating to their disease and may be invited to participate in relevant clinical trials once their data has been uploaded into the TREAT-NMD registry. Their data will be updated annually and stored indefinitely, or until they request their data to be removed.

5.0 DATA COLLECTION AND SUBMISSION

The data will be collected via an online form and will be stored in a central UK registry on the TREAT-NMD secure server located at Newcastle University. Initial data collection will include nine 'mandatory questions' including demographic information, SMA diagnosis, genetic results and current condition. A further six

'highly encouraged questions' focus on family history, ventilation, other registries and more specific information on their disease (Appendix 1).

One of the purposes of the SMA national registry is to define the UK SMA population and since, at the time of enrolment, patients will be at various stages of their disease course and medical care patients will be invited to update their records on a yearly basis again via an online form at this time they will also be given the opportunity to remove their data from the registry.

6.0 QUALITY ASSURANCE OF DATA

Patient personal and medical data will be kept for an indefinite period at Newcastle University in the UK, under the responsibility of Professor Hanns Lochmüller. This data will be subject to the regulations on data protection (national laws related to EU directive 95/46) and all information we receive from patients will be treated confidentially. The information will be encrypted and stored on a secure server located at Newcastle University in the UK.

Any future publications based on data collected via the registry will follow strict guidelines with respect to non publication of patient identifiable information.

Third parties wishing to have access to data in the TREAT-NMD European registry (such as researchers or companies planning clinical trials or conducting research on new therapies) will only have access to anonymous information identifiable only by a code. Before they are granted access even to this anonymous information, they will have to have the approval of an Ethics Committee. Patient data will not be made available to employers, governmental organizations, insurance companies, and educational institutions, or to a patient's family member or doctor.

7.0 STATISTICAL METHODS AND DATA REPORTING

Data will be analysed and reported periodically and upon individual requests from approved researchers. Baseline demographic and background variables will be summarised and will be made available to the neuromuscular community via the TREAT-NMD website. Access to more detailed information will be controlled by a password protected area of the website, which will enable restricted levels of access.

8.0 INSTITUTIONAL REVIEW BOARD/ INDEPENDENT ETHICS COMMITTEE

This protocol, the Patient Information and Authorisation (Appendix 2) and relevant supporting information should be submitted to an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) for review and approval. However since no experimental procedures are included in the protocol, the committee chairperson may decide that a full IRB or IEC review is not warranted. It is often only necessary to approve the Patient Authorisation.

8.1 Patient Authorisation/Consent

For every patient, appropriate patient authorisation/consent will be obtained according to national regulations and other state and local laws relating to medical information before data is submitted to the UK SMA Registry, this authorisation will also enable the encrypted data to be transferred to the TREAT-NMD European Registry. This will be clearly explained to the patient in the patient information sheet (Appendix 2) which will be given to the patient to read and consider prior to enrolment.

9.0 PATIENT CONFIDENTIALITY

Patients will be invited to register on the UK TREAT-NMD SMA database. If they choose to send their personal and medical data to the UK national registry, it will be stored in accordance with the Data Protection Act 1998 and pseudonymized. Encrypted data will then be transferred to the European registry where access will be available to international researchers. Researchers are, however, only permitted access to the data if they have approval by an IRB/ethics board and the TREAT-NMD coordinators. If researchers believe a UK patient meets a trial's criteria and might benefit from participation in the trial, they will contact the UK Principal investigator and /or the National curator. The UK principal investigator will then de-code the data and forward information on the trial to the patient. The patient's name or any other personal information will not be given to these researchers.

10.0 PATIENT DISCONTINUATION

Patient participation is voluntary. The patient may decline to participate or withdraw consent for their data to be stored on the register at any time without prejudice. Patients will be reminded that they may remove their data from the register on a yearly basis, when they are contacted to update their record.

11. REGISTRY SPONSOR

The UK SMA Registry is jointly sponsored by TREAT-NMD and the Jennifer Trust. TREAT-NMD reserves the right to discontinue the registry at any time.

Appendix 1 - SMA Self Report Form

Appendix 2 - Patient Information and Consent Form

Appendix 3 - Instructions for Self Report Form

Appendix 4 - Patient Information about TREAT-NMD and the SMA registry