



TREAT-NMD update for care and trial sites

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Introduction



The 200 clinical sites that make up the TREAT-NMD Care and Trial Sites Registry form a network that is unique in the neuromuscular field. We are committed to developing this powerful resource in a way that benefits everyone involved and are keen to keep in close contact with all PIs to keep you informed about TREAT-NMD activities and other news of importance to the neuromuscular field. This update gives you an overview of some of the activities that are of relevance to you and your sites, and we encourage you to read through it and come back to us with your queries and suggestions.



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About the Care and Trial Sites Registry

The TREAT-NMD Care and Trial Sites Registry (CTSR) is a database of clinical sites and medical centres set up by the TREAT-NMD Clinical Trials Coordination Centre in Freiburg to provide a valuable source of information about the experience, facilities, equipment and personnel of sites worldwide caring for neuromuscular patients.

Its primary focus is on collecting information that will enable the selection of sites with the expertise to take part in clinical trials. A second key aim is to develop an infrastructure for disseminating information on recent developments in the neuromuscular field and improving networking. On the final page of this document you can see an overview of the current status of the registry and the breadth of information it contains.

Registered sites benefit from:

- Updates regarding neuromuscular disease diagnosis and care
- Information about planned and ongoing trials
- Details of outcome measures and systematic reviews
- Opportunities for making use of the trial sites infrastructure for your own research or trials
- Training and education opportunities
- Advice and support with clinical trial development and funding possibilities
- Streamlined interaction with industry, patient organizations and regulators



TREAT-NMD update for care and trial sites

Industry enquiries

From the enquiries sent out to registered CTSR sites in recent months, you will be aware that TREAT-NMD is increasingly working with the pharmaceutical companies who are planning trials in the neuromuscular field. These companies recognise that the TREAT-NMD patient registries and the CTSR are a valuable source of information that assists them with their trial planning.

How feasibility enquiries work

- Company contacts TREAT-NMD with a request for feasibility data
- Specific terms of the enquiry are written into an agreement with the company
- CTSR assesses whether additional information is required from trial sites and requests updates via online questionnaire if necessary
- CTSR filters results according to requested criteria
- Sites meeting the criteria are contacted to confirm they are willing to release data to the company
- Company receives report including contact details of PIs
- Trial sites receive feedback on what has been sent to companies
- Company follows up with sites directly

In all its work with industry, TREAT-NMD's aim is to provide companies with the information they need so that trials can take place more quickly and easily. It's important to note that we do not make deals on behalf of the trial sites in the CTSR or take away any of their autonomy. Instead, we aim to act as a trusted intermediary, helping to put companies directly in contact with the sites who best meet their needs. We strongly believe that by being part of the CTSR, sites will be better informed about industry plans and more likely to be approached by companies to take part in trials.

An example: the Prosensa enquiry

In summer 2009, Prosensa contacted TREAT-NMD for assistance with their upcoming pivotal trial for their lead compound PRO-051, an antisense therapy for Duchenne muscular dystrophy that aims to restore the reading frame of the DMD gene in boys with mutations amenable to skipping of exon 51. In addition to an enquiry on eligible patient numbers through the DMD global patient registry, Prosensa requested details of trial sites in a certain set of countries meeting certain criteria (sites seeing more than a certain number of DMD patients, with echocardiography facilities, a certain level of muscle biopsy experience, GCP training etc.), and also asked to know which of these sites were involved in the PTC trial or had other phase II/III trial experience. CTSR staff contacted all sites to ask them to ensure their details were up to date, and then filtered the results according to Prosensa's criteria. After gaining consent from all the sites concerned to release their data to Prosensa (either individually or via the general consent option in the questionnaire), the CTSR sent Prosensa a full report giving a summary of the requested information on each site plus contact details for the PI. Prosensa are now in the process of shortlisting and contacting sites directly for their trial, which is due to start in the first quarter of 2010.










Keeping your data complete and up to date means the companies who contact TREAT-NMD can find out about your facilities and expertise without requiring you to fill in additional feasibility questionnaires. We encourage all sites to fill in the questionnaire as fully as they are able. Check your data online at www.treat-nmd.eu/trialsites and if you have any questions please contact kathrin.gramsch@uniklinik-freiburg.de or adrian.tassoni@uniklinik-freiburg.de



TREAT-NMD update for care and trial sites

How TREAT-NMD is assisting with clinical trials: trial timelines

In one form or another, TREAT-NMD is assisting the majority of companies currently planning or running neuromuscular trials. It is also involved in investigator-led research. An overview of the support provided and an idea of the timelines involved in some of the ongoing and upcoming trials is provided in the table below.

Trial/company	Drug/disease	How TREAT-NMD is involved	Timeline
 ACCELERON PHARMA	ACE-031 DMD, FSHD	<ul style="list-style-type: none"> SAB setup for DMD program TREAT-NMD partners on advisory board 	Phase I healthy volunteer study completed Q3 2009. Phase II study in planning stage
 AVI BioPharma	AVI-4658 DMD	<ul style="list-style-type: none"> TREAT-NMD partners on advisory board TREAT-NMD partners as trial sites Patient registries enquiry (patient numbers; frequency of top 5 exon skippable mutations) 	Phase IIa study (2 UK centres) due to finish Q4 2009 Pivotal trial due to begin Q2/3 2010
 BIOMARIN	BMN-195	<ul style="list-style-type: none"> SAB setup for DMD trial under negotiation 	Phase I trial planned to start Q1 2010
 PROSENSA	PRO-051 DMD	<ul style="list-style-type: none"> TREAT-NMD partners on advisory board Patient registries enquiry (DMD patients meeting trial inclusion criteria) CTSR enquiry and provision of site contact details for pivotal trial site selection 	Phase IIa trial results announced Q3 2009 Pivotal trial due to begin Q1 2010
 PTC THERAPEUTICS	Ataluren DMD	<ul style="list-style-type: none"> TREAT-NMD partners on advisory board TREAT-NMD partners as trial sites TREAT-NMD conducted European arm of clinical evaluator training Patient registries enquiry (patients with nonsense mutations) 	Multicentre phase IIb trial ongoing; results expected Q3 2010 Extension study enrolment ongoing for patients already part of IIb trial
 santhera Pharmaceuticals	Catena/ Sovrima DMD Omigapil CMD	<ul style="list-style-type: none"> TREAT-NMD partner TREAT-NMD partners on advisory board TREAT-NMD will assist with European arm of physiotherapist training TREAT-NMD assisting with application for FP7 funding for CMD trial 	12-month pivotal trial (DELOS) initiated in September 09 and will enrol up to 240 patients in 25 centres in Europe and N. America.
 TROPHOS The neuron company	TRO19622 SMA	<ul style="list-style-type: none"> TREAT-NMD Clinical Trials Coordination Centre to perform site selection and protocol development for phase II efficacy study through collaboration with Trophos and CRO LabConsult Feasibility information will be collected through CTSR and SMA patient registries 	Phase II trial to begin in 2010
FOR-DMD NIH-funded trial to assess steroid dosing regimes	Prednisone/ Deflazacort	<ul style="list-style-type: none"> Collaboration with US Muscle Study Group TREAT-NMD to coordinate European trial site recruitment (CTSR sites will be asked to apply) and regulatory submissions TREAT-NMD to conduct European arm of clinical evaluator training 	Site recruitment, regulatory submissions etc. to begin 2010; patient recruitment planned to begin 2011.

TREAT-NMD update for care and trial sites

Services for investigators conducting research and academic trials

Through the TREAT-NMD infrastructure, investigators registered with the care and trial sites registry have access to a wide range of trial and research-related tools and services.

TREAT-NMD Advisory Committee for Therapeutics (TACT)

The TREAT-NMD Advisory Committee for Therapeutics is an expert body set up by TREAT-NMD to provide transparent and consistent guidance and advice to the neuromuscular community on the prioritisation and readiness of potential new therapies for neuromuscular diseases. Clinicians and researchers working on new therapies with promising preclinical results can contact TACT for advice on the steps to be taken to move into clinical trials, or for an unbiased appraisal from leading experts of the “readiness” of their therapy for this step.

For further information visit www.treat-nmd.eu/TACT or contact emma.heslop@ncl.ac.uk.

TREAT-NMD Registry of Outcome Measures (ROM)

The Registry of Outcome Measures is a freely accessible and regularly updated online resource that is a convenient first stop for important baseline information about existing outcome measures, with directions to key points of contact and comprehensive information. It contains detailed summary of each outcome measure, including a description, availability information, contact details for providers (e.g. device suppliers, distributors of outcome measures), and references to related documents including manuals and training videos. Outcome measure records are created and maintained using an online form and input is welcomed from anyone with an appropriate understanding of a particular measure – whether the person or group responsible for developing the measure or medical practitioners with a sound working knowledge of it through use or research. For further information visit www.treat-nmd.eu/ROM or contact joanne.auld@kcl.ac.uk.

Patient registries

The TREAT-NMD patient registries described on the following pages are also open to enquiries from academic colleagues, and CTSR PIs are invited to make use of the registries for their own research questions. Although the patient registries do not collect extensive natural history data, much valuable information can be gleaned from the focused dataset collected, and examples of this have already been presented at international meetings (see www.treat-nmd.eu/smaregistrycomparison for one such study).

For further information contact hanns.lochmuller@ncl.ac.uk.

Regulatory affairs database

The regulatory affairs database is a valuable source of advice to investigators involved in the planning of clinical trials. The current version contains details of national legislation from countries across Europe. US regulations are planned to be incorporated in future. European regulations and other important international guidelines (e.g. from ICH and EMEA) are also available.

For further information visit www.treat-nmd.eu/regulatoryaffairs or contact sebastian.geismann@uniklinik-freiburg.de

GCP and trial design training

The Clinical Trials Coordination Centre in Freiburg offers an annual training course that combines expert training in the fundamentals of trial design in rare diseases with accredited GCP training. The next course is scheduled for 24th -26th of June 2010.

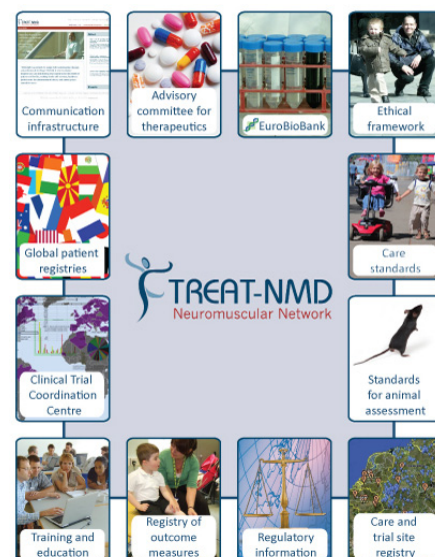
For further information contact kathrin.gramsch@uniklinik-freiburg.de.

Standards of care guidelines

Receiving the best care can dramatically improve patients' quality of life and even prolong life expectancy. Variations in care standards between and even within countries not only impact on quality of life but also make clinical trials of promising new treatments much harder to carry out, as the comparability of results from different centres is compromised. Collaborations led by the International Coordinating Committee for Spinal Muscular Atrophy and the US Centres for Disease Control and Prevention have put together specialist groups to draw up international consensus documents on standards of care. The SMA care standards, including a family-friendly version, have been publicised through the TREAT-NMD website and are sent out through many of the national SMA patient registries in a handy brochure form. The DMD standards, entitled *The Diagnosis and Management of Duchenne Muscular Dystrophy*, are now available online prior to their official printed publication in the *Lancet Neurology* in January 2010, and again a family-friendly version drawn up in close collaboration with Duchenne patient advocacy groups will be issued via the TREAT-NMD website in January 2010.

SMA care standards: www.treat-nmd.eu/sma-care

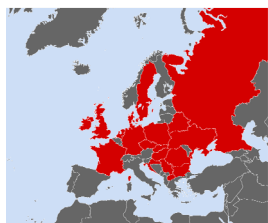
DMD care standards: www.treat-nmd.eu/dmd-care



TREAT-NMD update for care and trial sites

Future developments and calls for volunteers

CARE-NMD – a new project for Duchenne care



We are currently in negotiations with the European Commission’s Executive Agency for Health and Consumers (EAHC) over the funding of a new project focusing on implementation of care recommendations drawn up in the international consensus process described above. The CARE-NMD project aims to assess the current state of Duchenne care and patient quality of life in countries across Europe and – through training, education and dissemination – work towards making the best care available to all patients. This is also being used as a model for the roll-out of care standards for other neuromuscular conditions. The CARE-NMD project is likely to start in April 2010. For further information

contact janbernd.kirschner@uniklinik-freiburg.de.

Call for expert trainers

As part of their training and education activity within TREAT-NMD, the ENMC are requesting contacts from experienced clinicians and scientists able to deliver training on topics ranging from diagnostics to physiotherapy to care standards.

For further information see www.treat-nmd.eu/trainingcall or contact Katelijne Senden (senden@enmc.org).

Additional diseases

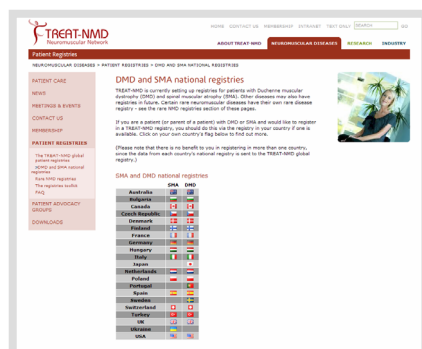
TREAT-NMD began with a focus on two flagship diseases, DMD and SMA, and similarly the CTSR started out collecting details primarily from paediatric neuromuscular sites on paediatric conditions. However, with the extension of the TREAT-NMD tools and services to additional diseases including those predominantly affecting the adult population (such as LGMD, DM and FSHD), we are also beginning outreach to adult sites and specialists. We strongly encourage all our adult neurology colleagues across the world to register their sites and complete our questionnaire at www.treat-nmd.eu/trialsites.



Publicising the CTSR

In 2010 we aim to increase the profile of the CTSR as a global network of sites with neuromuscular expertise – something that we hope will be of real benefit to all registered sites. As part of this we plan to include a world map of registered sites with some basic data about the PIs, and we’ll be contacting all PIs in the New Year to request the appropriate permissions from you all.

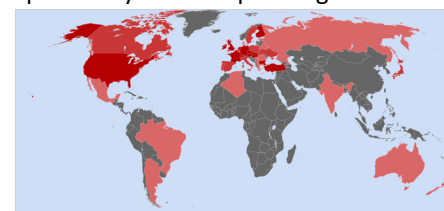
TREAT-NMD patient registries for DMD and SMA



The TREAT-NMD patient registries were set up primarily with future trials and therapies in mind. The global registries for DMD (with over 10000 patients) and SMA (over 1000 patients) are recognised as the leading resource for trial planning and recruitment in these diseases at an international level and are already being used by pharmaceutical companies for this purpose. They function on the basis of multiple national systems (currently 30 countries worldwide) feeding into an international database. The national systems all collect the same streamlined, internationally harmonised core dataset that includes key information facilitating trial planning (such as inclusion/exclusion criteria based on ambulation, cardiac status, medication use etc.) and enabling patient recruitment. The registries have a clear ethos of patient involvement, feedback and consent together with ethical governance and oversight, and include the possibility of incorporating broader

datasets/additional modules on a national level for natural history and longitudinal data collection. In many cases patients are able to self-report the majority of their data, but a curation stage is built in for the genetic test results to ensure the reliability of the data.

A full list of all the existing national registries can be found at www.treat-nmd.eu/nationalregistries. We strongly encourage all CTSR sites to ensure their DMD and SMA patients are registered in their national registry, and you are very welcome to get in touch with either the national registry curators themselves via the contact information available through the above URL or info@treat-nmd.eu for more details.



DMD patient registries: 30 countries, 10000 patients



TREAT-NMD update for care and trial sites

New patient registries for other conditions



The success of the DMD and SMA registries has inspired other groups to work with TREAT-NMD to set up registries for other conditions. An overview of these is provided below, together with links to further details, and anyone interested in finding out more is also invited to contact Hanns Lochmüller (hanns.lochmuller@ncl.ac.uk) for further information.

Myotonic dystrophy type 1 (DM1)

After a workshop in Naarden bringing together DM1 experts already involved in national registry initiatives worldwide, agreement was reached on the launch of an international DM1 registry using the DMD and SMA model (national registries feeding into a global database). A core dataset has been defined and national registries are currently implementing these items into their systems, with the global registry due for launch in summer 2010.

More information: www.treat-nmd.eu/DM1registry



FKRP mutations

This gene-specific registry collects data from patients suffering from FKRP mutations (most often manifesting as LGMD2I but also MDC1C, Walker-Warburg syndrome and Muscle-Eye-Brain disease). As FKRP mutations are less common than diseases like DMD and SMA, this is a single international registry for all patients worldwide, and involves a combination of patient self-report and specialist clinician report.

More information: www.FKRP-registry.org

Congenital muscular dystrophies

Meetings between TREAT-NMD representatives, CMD experts, registry experts and representatives of the Cure CMD patient organisation resulted in the launch of the CMD International Registry (CMDIR) in August 2009. This registry uses many of the TREAT-NMD principles of streamlined data collection, patient consent, patient feedback etc. In addition, although the CMDIR collects data from patients with any form of CMD including those without a diagnosed genetic mutation, a mutual agreement on harmonisation of core data elements allows exchange of data with TREAT-NMD locus specific databases (such as the FKRP registry above).

More information: www.cmdir.org

Myotubular/centronuclear myopathy

A European patient registry for myotubular myopathy is currently being established by the UK patient organisation the Myotubular Trust with guidance from TREAT-NMD. This registry has adopted many of the principles of the TREAT-NMD, and TREAT-NMD has also facilitated the development of links with US plans in the same area so as to ensure an internationally harmonised effort.

More information: http://www.myotubulartrust.com/research_patientregistry.htm

Charcot-Marie-Tooth disease

Following discussions at the 168th ENMC workshop on outcome measures and clinical trials in CMT, plans are being taken forward for an international CMT patient registry to be developed in collaboration with TREAT-NMD.

More information: hanns.lochmuller@ncl.ac.uk

Other neuromuscular conditions

A number of other national and international initiatives are already in place for various rare neuromuscular disorders. Many of these were discussed at the 157th ENMC workshop on patient registries for rare inherited muscular disorders, and further details together with an inventory of existing initiatives can be found on the TREAT-NMD website.

More information: http://www.treat-nmd.eu/rare_registries



TREAT-NMD update for care and trial sites

Update on registered sites

With almost 200 sites in 44 countries worldwide now registered, we can really start to see the immense power of this global network of centres which in total care for over 25000 patients with a range of neuromuscular conditions.

