9 April 2010
TREAT-NMD newsletter no. 75
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# welcome

Welcome to the 75th Newsletter from TREAT-NMD.

This week's newsletter includes...

- an update on the global registries

- the release of the non-confidential TACT reports

- a request for volunteers to translate the DMD family guide

- a workshop report about preclinical testing in SMA

We would like to thank those who have contributed to this week's edition. This newsletter relies on input from our readers. If you have anything you wish to be included in the next newsletter please contact us at info@treat-nmd.eu

# at a glance...

23-24 Apr 2010 2nd Joint Meeting Belgian-Dutch Neuromuscular Study Club and German Reference Center for Neuromuscular Diseases of the DGNN - Valls, Netherlands

2-7 May 2010 International Child Neurology Congress 2010 - Cairo, Eygpt

10 May 2010 The George Karpati Symposium on Neuromuscular Disease: Innovation and Application, Montreal, Canada

13-15 May 2010 5th European Conference on Rare Diseases - Krakow, Poland

17-19 Jun 2010 International Conference on Neuromuscular Diseases - Sao Paulo, Brazil

19-23 Jun 2010 20th Meeting of the European Neurological Society - Berlin, Germany

24-27 Jun 2010 Parent Project Muscular Dystrophy Annual Conference - Denver, Colorado, USA

24-27 Jun 2010 Families of SMA Annual Conference - Santa Clara,


## Update on the TREAT-NMD Global Patient Registries

Working with many patient organisations across the world, TREAT-NMD has helped to create national gene-specific patient registries with future clinical trials and therapies in mind. These national registries contribute to the global registries for Spinal Muscular Atrophy (SMA) and Duchenne Muscular Dystrophy (DMD; including Becker Muscular Dystrophy) and are recognised as a leading international resource for clinical trial feasibility and planning. The registries are increasingly used by industry and are also open to enquiries from academics. Moreover, the registries are appreciated as a resource for reliable and up-to-date information by patients and their families.

For patients, the registries are a valuable way of receiving information and feedback related to their condition and of getting connected to the research community. Patients who are potentially eligible for specific clinical trials have consented to being contacted about those trials. They are contacted only by their clinician or their national registry (which is feeding anonymised data into the global, gene-specific registry), not by TREAT-NMD or the global registry itself, and not by pharmaceutical companies or researchers. Each national SMA and DMD registry (that is part of the TREAT-NMD global registries) is collecting a harmonised core dataset that includes the patients' precise genetic mutation and trial-relevant clinical information. The medical data are checked by national curators for completeness and accuracy.

The national and global SMA and DMD registries are governed by a charter that helps to define best practice available. For the national registries, this means for example that patients need to be consented, their medical data be updated frequently, patients be given appropriate feedback and they have the right to withdraw their registration at any time. At the global registry level, third-party access is also governed by an oversight committee (the "TGDOC - TREAT-NMD Global Database Oversight Committee") consisting of representatives of the contributing national registries, which includes many patient organisations, as well as representatives of other patient organisations, the TREAT-NMD Project Ethics Council and the TREAT-NMD Clinical Trial Coordination Centre. Patient recruitment into multi-national clinical trials through the national registries is also governed by TREAT-NMD and national registries best-practice guidelines aimed at setting a standard for effective and ethical communication to patients.

Prior to the launch of the TREAT-NMD network in January 2007, the only existing SMA patient registry was the International SMA Registry (Indiana University, USA). For DMD, four patient registries existed worldwide: in the UK (Action Duchenne), U.S.A. (UDP Registry, Utah), France (INSERM) and the Czech Republic (Czech Duchenne Parent Project), all collecting different datasets and requiring the input from several professionals such as clinicians, geneticists and physiotherapists, which led to a lack of international harmonisation.

Today, 33 harmonised SMA registries covering 33 countries have been set up, with a third of them fully operational. These registries feed into the global TREAT-NMD patient registry for SMA, which currently contains information on more than 2,000 SMA patients worldwide. For DMD, 42 registries in 41 countries form a global network of harmonised national DMD registries, of which 19 are fully operational. Together they hold information on more than 10,000 genetically confirmed DMD patients across the world.

The global registries can provide information based on different types of enquiries once approved by the oversight committee (TGDOC). Feasibility enquiries request anonymised, aggregate data in the form of patient numbers, usually by country of residence. Moreover, assistance for the recruitment of patients into multi-national clinical trials may be requested through the registries. In this case, the trial sponsor needs to first seek approval from the local ethics boards at the institutions of the countries involved, before the enquiry is addressed by the global registry. After approval by the ethics boards and the TGDOC, the global registry retrieves the anonymised datasets of the potentially eligible patients who fulfil all the trial-inclusion criteria according to the information held in the registries. This

California, USA

19-23 Jul 2010 12th International Congress on Neuromuscular Diseases - Naples, Italy

12-16 Oct 2010 World Muscle Society International Congress - Kumamoto, Japan

12-13 Nov 2010 Action Duchenne 8th Annual Conference - London, UK

Please note: This is only a selection of upcoming meetings. To see all our listed meetings click here.

information is passed on to the national registries that can identify the patients and contact them about the trial.

From February 2009 until March 2010, the TREAT-NMD global patient registries for DMD and SMA received 5 feasibility enquiries from different pharmaceutical companies, 4 enquiries for the DMD registries and 1 for the SMA registries. Objectives of these enquiries included marketing and trial feasibility and trial planning. Anonymised, aggregate data on patient numbers in Europe, North America and worldwide were requested, including information on specific mutations, and clinical parameters relevant for trials (such as age, ambulation status, ventilation, cardiomyopathy, previous and current trial participation). For DMD there are plans for clinical trials using exon skipping. More than 2,000 DMD patients of all ages in the global registry are amenable to the skipping of 5 particular exons, while more than 400 patients aged 5-16 years are amenable to exon 51 skipping. In addition, almost 800 patients worldwide carry a nonsense mutation. Out of the genetically confirmed SMA patients in Europe, more than 800 are of SMA Type 2 or 3 and aged 3-25 years. We anticipate additional enquiries into the registries by both industry and academic investigators as this resource is increasingly recognised as the primary access point to obtain relevant and accurate information on patients for multi-national clinical trials.

Following the success of the TREAT-NMD patient registries for DMD and SMA, patients, patient organisations and professionals concerned with other inherited neuromuscular conditions have approached TREAT-NMD to assist them in setting up harmonised national and/or global registries. These include Myotonic Dystrophy (DM), Charcot-Marie-Tooth disease (CMT), Facioscapulohumeral Muscular Dystrophy (FSHD), Congenital Muscular Dystrophy (CMD), Myotubular Myopathy, Nemaline Myopathy and dystrophies due to Fukutin-Related Protein (FKRP) mutations.

Information on the national and TREAT-NMD global patient registries can be found on the TREAT-NMD website under Patient Registries and subsequent links.

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## TACT Non Confidential Meeting Reports Available

In February TACT evaluated three proposals at its first review meeting. These included:

1. Losartan – submitted by Dr Christopher Spurney, Children's National Medical Centre, Washington DC, USA
2. Isosorbide plus Ibuprofen – submitted by Dr Emilio Clementi and Dr Grazia D'Angelo, H Sacco, University Hospital, University of Milano, Italy
3. Flavocoxid –submitted by Dr Sonia Messina and Prof Giuseppe Vita, University of Messina, Italy

The TACT reports with recommendations were sent to the applicants within 6 weeks following the meeting - by the 19th March. The corresponding three non-confidential reports, approved by the applicants, have now been uploaded to the TACT webpage on the TREAT-NMD website. We feel it is important that applicants agree to a non-confidential TACT recommendations summary that can be made publicly available, but recognise that some will prefer to limit distribution only to those parties who have signed a confidentiality agreement. Having the flexibility to allow this, we hope, will broaden the number of applicants willing to seek TACT advice.

TACT and the TREAT-NMD secretariat asked the applicants for feedback on the TACT review process. The feedback we receive will be taken into account as we move forward with TACT and a number of the comments received can be found below:

**Dr. Christopher Spurney, Children's National Medical Center, Washington DC, USA**
Treatment of early cardiac systolic dysfunction in Duchenne muscular dystrophy with lisinopril or Losartan: a prospective, randomized, blinded, crossover trial.

*"The TACT process was extremely beneficial. It was timely, fair and well organized. The TACT committee provided experts from multiple fields and each provided unique insight on the proposal. We received a breadth of comments that will strengthen our proposal. In its entirety, the TACT review likely will save us over a year's time in moving our clinical protocol forward. I highly recommend the TACT committee."*

**Dr. Emilio Clementi and Dr. Grazia D'Angelo, H Sacco University Hospital, Milan, Italy**
A pharmacological treatment for muscular dystrophy combining NO-releasing and non steroidal anti-inflammatory drugs.

*"In general, we have had a very good impression and we do think it is a very valuable instrument to help clinicians and scientists to design sensible clinical trials in muscular dystrophy. TACT should be highly publicised and possibly put into some sort of official agreement with the regulatory agencies".*

**Professor Giuseppe Vita and Dr. Sonia Messina, University of Messina, Messina, Italy**
Randomized double-blind placebo-controlled trial of flavocoxid in Duchenne muscular dystrophy.

*"All the process since the proposal submission to the final report has been very helpful for us. Your comments highlighted relevant issues of the proposal and will surely help us to strengthen the final version of the project".*

This first meeting provided valuable perspective on how to further clarify and fine tune the entire TACT review process. Refinements have already been or will be implemented for the second review meeting in June 2010.

We hope that the advisory role of TACT is becoming clearer to the community and that this will encourage future applicants to apply to TACT, assure the community that the reviews are useful and effective and encourage funding organizations to engage with TACT so that we can identify a way to synergize with their grant review processes.

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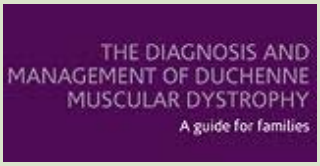
## Diagnosis and Management of DMD - Translation of the Family Guide




The family guide has been well received since its launch in the last newsletter with a number of volunteers offering to translate the guide. TREAT-NMD would like to gather a comprehensive list of translations and would therefore like to put a call out for volunteers to translate the document into other languages.

The “print friendly” version of the family guide will be the most widely available, with some patient organisations also producing the printed brochures. Please visit the website for a full list of ongoing translations as well as languages that are still required. We want to thank our current volunteers for offering to translate the family guide. If you are interested in volunteering to translate all or some of the family guide into a language that hasn’t yet been covered then please contact Karen Rafferty at TREAT-NMD.

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## International workshop - Preclinical testing in SMA - Zurich, Switzerland. 29-30th March 2010

One of the activities of TREAT-NMD is to harmonize experimental methods used to evaluate the efficacy of a test drug in animal models of disease and thereby reduce duplication of efforts and inconsistency of data that ultimately delay the progression of candidate molecules into the clinic. TREAT-NMD, in collaboration with the Wellstone Centres in the US, has already created a collection of standard operating procedures (SOPs) for animal models of DMD. TREAT-NMD partner organisations, Santhera and the University of Basel, recently organised a workshop to take a major step towards assessing this issue for mouse models of SMA with the aim to produce SOPs for use in the field of SMA research and to aid the assessment of new potential therapies in mouse models of SMA.

Thirty key SMA researchers convened last week in Zürich to discuss endpoint measurements in mice models and to reach a consensus as to which endpoints are particularly relevant to the clinical situation when assessing the preclinical efficacy of a candidate drug.

The meeting was also attended by four leading clinicians in the field and representatives from two patient organizations and industry. Moreover, it was agreed to form expert working groups extended to the wider community to compile standard protocols for each of the most important endpoints discussed at the workshop.

Once finalized, after receiving further input from the community, these protocols will be made accessible through the TREAT-NMD web site in the hope that the widespread use of standardized procedures will help increase the comparability of studies across laboratories. Both the level of expertise and the motivation of the attendees were impressive.

The workshop, organised and supported by TREAT-NMD, represents an important step towards a more efficient translation of preclinical research to the clinic in the process of drug development.

An extensive article about this workshop will be submitted for publication in Neuromuscular Disorders in the near future. For further information please contact Raffaella Willmann.

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