Swiss-Reg-NMD

UNIVERSITÄT BERN

Swiss Registry for Neuromuscular Disorders

Annual report for 2018

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1. Executive Summary

The registry for patients with Duchenne/Becker Muscular Dystropies (DMD/BMD) and patients with Spinal Muscular Atrophies (SMA) started in 2008. In those days, the main aim of the registry was to allow patients access to new drugs in Switzerland. In 2016, it became clear that the registry had to undergo changes to ensure it can address today's questions in the field of neuromuscular diseases as well as to assure long-term data quality and security. For this reason, the registry moved to the Institute of Social and Preventive Medicine (ISPM) in Bern in 2017. The registry is now called the "**Swiss Registry for Neuromuscular Disorders**" (Swiss-Reg-NMD). Its long-term goal is to improve the care and well-being of people with neuromuscular diseases in Switzerland.
In 2018, we obtained approval from the Cantonal Ethics Committee of Bern for the Swiss-Reg-NMD. Because of this new ethics approval, we are currently approaching all patients who were previously included to ask their consent for the Swiss-Reg-NMD. The registry is now allowed to include additional neuromuscular disorders in addition to DMD/BMD and SMA. In 2018, the reporting of patients with Merosin-negative congenital muscular dystrophy (MDC1A) started and more diseases should follow.

Between 2008 and 2018, 372 patients with DMD/BMD and SMA have been reported to the registry. Of these, 325 have not been reported as deceased: 177 with DMD, 51 with BMD or intermediate forms, and 97 with SMA. Also, 7 cases with MDC1A were reported in 2018.

Since 2008, more than 60 patients have been included in clinical trials in Switzerland and abroad. As in previous years, the registry answered requests from companies to assess potential trial recruitment in 2018. During this year, 9 DMD patients were enrolled in the TAMDMD trial and 6 further patients (DMD and SMA) were enrolled in other trials.

In addition to facilitating the inclusion of patients into trials, an important new focus of the Swiss-Reg-NMD is to collect information to assess the effectiveness and side effects of new drugs after their marketing approval. To this end, the medical data that are to be collected in the clinics must be clearly defined. We have now defined this data for SMA and created a form for data collection. We will do the same for DMD/BMD in 2019.

The organisational structure of the registry was further formalised during 2018: The new steering board includes physicians from most large clinical centres in Switzerland. Together with the small team at ISPM they will give the Swiss-Reg-NMD long-term stability and direction.

In 2018 the Swiss-Reg-NMD received funding from the 'Schweizerische Muskelgesellschaft'; the 'Association Suisse Romande Intervenant contre les Maladies neuro-Musculaires'; the 'Associazione malattie genetiche rare della svizzera italiana', the 'Schweizerische Stiftung für die Erforschung der Muskelkrankheiten' and from PTC Therapeutics. We thank these organisations for their support. A major challenge for 2019 is to secure sufficient funding for the registry to complete the planned changes as well as continue running the registry.

Zusammenfassung

Das Schweizer Register für Patienten mit Muskeldystrophie Duchenne/Becker (DMD/BMD) und Spinaler Muskelatrophie (SMA) wurde 2008 gegründet. Damals war das Hauptziel des Registers, Patienten Zugang zu neuen Medikamenten in der Schweiz zu ermöglichen. Im Jahr 2016 wurde klar, dass das Register modernisiert werden muss, um die heutigen Fragen zu neuromuskulären Erkrankungen beantworten und die langfristige Datenqualität und -sicherheit gewährleisten zu können. Das Register ist deshalb 2017 an das Institut für Sozial- und Präventivmedizin (ISPM) in Bern verlegt worden und heisst neu "S**chweizer Register für neuromuskuläre Erkrankungen**" (Swiss-Reg-NMD). Das langfristige Ziel ist die Behandlung und das Wohlbefindens von Menschen mit neuromuskulären Erkrankungen in der Schweiz zu verbessern.

Im Jahr 2018 haben wir die Bewilligung der Kantonalen Ethikkommission Bern für das Swiss-Reg-NMD erhalten. Aufgrund dieser neuen Ethik-Zulassung wenden wir uns derzeit an alle bisher eingeschlossenen Patienten, um ihre neue Zustimmung für die Swiss-Reg-NMD einzuholen. Wir dürfen nun neben DMD/BMD und SMA weitere neuromuskuläre Erkrankungen einschliessen. So begann im Jahr 2018 die Meldung von Patienten mit Merosin negativer Muskeldystrophie (MDC1A); weitere Erkrankungen werden folgen.

Ende 2018 waren 372 Patienten Teil des Registers. 325 von ihnen sind nicht als verstorben gemeldet: 177 mit DMD, 51 mit BMD oder intermediären Formen und 97 mit SMA. Zusätzlich wurden bereits 7 Patienten mit MDC1A eingetragen.

Seit 2008 konnten mit der Unterstützung des Registers mehr als 60 Patienten in klinische Studien im In- und Ausland eingeschlossen werden. Wie in den Vorjahren beantwortete das Register im Jahr 2018 Anfragen von Unternehmen, zur Durführbarkeit klinischer Studien in der Schweiz oder um Patienten zu rekrutieren. In diesem Jahr wurden 9 DMD Patienten in die TAMDMD-Studie und 6 weitere Patienten (DMD und SMA) in andere Studien aufgenommen.

Neben dem Ziel die Studienteilnahme für Patienten zu erleichtern ist neu die Erfassung der Wirksamkeit und allfälliger Nebenwirkungen von neuen Wirkstoffen nach deren Marktzulassung ein zusätzliches wichtiges Anliegen des Swiss-Reg-NMD. Dafür muss klar festgelegt werden, welche medizinischen Daten in den klinischen Zentren erhoben werden sollen. Wir haben für SMA diese Daten nun definiert (angelehnt an international erhobene Daten) und ein Formular für die Datenerhebung erstellt. Das Formular für DMD/BMD folgt im Jahr 2019.

Wir haben im Laufe des Jahres 2018 auch die organisatorische Struktur des Registers weiter festgelegt: Der neue Vorstand besteht aus Ärzten und Ärztinnen der meisten grossen klinischen Zentren der Schweiz. Der Vorstand wird zusammen mit dem kleinen Team am ISPM dem Register langfristige Stabilität und Orientierung verleihen.

Im Jahr 2018 erhielt die Swiss-Reg-NMD finanzielle Unterstützung von der ‘Schweizerische Muskelgesellschaft’; der ‘Association Suisse Romande Intervenant contre les Maladies neuro-Musculaires’; der ‘Associazione malattie genetiche rare della svizzera italiana’, der ‘Schweizerische Stiftung für die Erforschung der Muskelkrankheiten’ und von PTC Therapeutics. Wir danken diesen Organisationen für ihre Unterstützung herzlichst. Eine große Herausforderung für 2019 besteht darin, eine hinreichende Finanzierung für das Register zu gewährleisten, um die geplanten Änderungen abzuschließen und das Register weiterzuführen.

Sommaire

Le Registre Suisse pour la Dystrophie Musculaire de Duchenne/Becker (DMD/BMD) et l'Amyotrophie Spinale (SMA) a démarré en 2008. A l'époque, l'objectif principal du registre était de faciliter l'accès des patients aux nouveaux médicaments en Suisse. En 2016, il fut clair que le registre devait subir des changements pour répondre aux questions actuelles dans le domaine des maladies neuromusculaires, ainsi qu'assurer la qualité et la sécurité des données sur le long terme. Pour ces raisons, le registre a été transféré à l'Institut de médecine sociale et préventive (ISPM) à Berne en 2017. Le registre se nomme désormais "Registre suisse des maladies neuromusculaires" (Swiss-Reg-NMD). Son objectif à long terme est d'améliorer les soins et le bien-être des personnes atteintes de maladies neuromusculaires en Suisse.

En 2018, nous avons obtenu l'approbation du Comité cantonal d'éthique de Berne pour le Swiss-Reg-NMD. En raison de cette nouvelle approbation, nous contactons actuellement tous les patients qui étaient déjà inclus, pour demander leur consentement actualisé pour le Swiss-Reg-NMD.

Le registre est maintenant autorisé à inclure d'autres maladies neuromusculaires, en plus de la DMD/BMD et de la SMA. En 2018, nous avons débuté la notification des patients atteints dystrophie musculaire congénitale avec déficit en mérosine (ou MDC1A en anglais), d'autres maladies devraient suivre.

Fin 2018, 372 patients étaient inscrits dans le registre. 325 d'entre eux n'avaient pas été déclarés décédés : 177 avec DMD, 51 avec BMD ou forme intermédiaire de dystrophinopathie, et 97 avec SMA. De plus, 7 patients atteints de MDC1A ont été nouvellement inclus.

Grâce au soutien du registre, plus de 60 patients ont été inclus dans des études cliniques en Suisse ou à l'étranger depuis 2008. Comme les années précédentes, nous avons répondu en 2018 aux demandes d'entreprises concernant la faisabilité d'études cliniques en Suisse. Cette année, 9 patients atteints de DMD ont été recrutés dans l'étude TAMDMD et 6 autres patients (DMD et SMA) ont participé à d'autres études.

L'un des objectifs du Swiss-Reg-NMD est d'analyser les effets des nouvelles thérapies. Pour cela, il est nécessaire de définir de manière précise les données médicales à collecter dans les centres cliniques. Ceci a été fait pour la SMA avec la création d'un nouveau formulaire de collecte de données. Le formulaire DMD/BMD suivra en 2019.

Nous avons en outre défini la structure organisationnelle du Registre en 2018 : Le nouveau conseil d'administration est composé de médecins de la plupart des grands centres neuromusculaires de Suisse. Le Conseil d'administration et la petite équipe à l'ISPM donneront une stabilité et une vision à long terme au registre.

En 2018, Swiss-Reg-NMD a reçu le soutien financier de la 'Muskelgesellschaft'; de la 'Association Suisse Romande Intervenant contre les Maladies neuro-Musculaires'; de la 'Associazione malattie genetiche rare della svizzera italiana', de la 'Schweizerische Stiftung für die Erforschung der Muskelkrankheiten' et de PTC Therapeutics. Nous tenons à remercier ces organisations pour leur soutien. L'un des principaux défis à relever en 2019 consistera à assurer un financement suffisant pour que le registre puisse mener à terme les changements prévus et poursuivre ses activités.

2. Introduction

Neuromuscular disorders (NMDs) are diseases that affect the functioning of the peripheral nervous system (motor neurons, nerves, neuromuscular transmission and muscle). Most have a genetic origin and all NMDs are rare diseases with few patients scattered across the country. Symptoms vary depending on the disease but commonly include muscle weakness, delayed motor development and/or functional impairment. In addition, patients may also suffer from chronic pain, intellectual impairment, problems with eating, or communication. Hence they require multi-disciplinary care. Symptoms often begin in childhood but can occur throughout life

Until recently only supportive treatment was available, but recent years have seen rapid developments. In 2017 the first treatment for Spinal Muscular Atrophy (SMA) was approved by Swissmedic, while for Duchenne Muscular Dystrophy (DMD) two compounds have received conditional approval in Europe and the US. Now that treatments are available, it is crucial to follow patients during treatment and monitor their motor outcomes and respiratory outcomes, as well as possible side effects and quality of life.

In 2008, the 'Swiss Patient Registry for Duchenne/Becker Muscular Dystrophy and Spinal Muscular Atrophie' was launched to allow Swiss patients to have access to new therapies by facilitating patients to be identified and contacted for trials. After nearly ten years of activity, this registry is now undergoing several major changes to make it suitable for the present and future needs of patient's organisations, health authorities and research organisations. This improved registry is now called 'Swiss Registry for Neuromuscular Disorders' (Swiss-Reg-NMD).

This report provides an overview of the activities of the Swiss-Reg-NMD in 2018, including the progress made towards improving the system, as well as number of patients registered and selected for studies. We will start by describing the registry: its aim, how it is organised, and how it is funded; and end by outlining the next steps to make the registry fully functional.

3. Description of the Swiss-Reg-NMD

3.1. Objectives

The main objective of the Swiss-Reg-NMD is to facilitate the inclusion of Swiss patients in therapeutic trials and to improve, on the basis of a better knowledge, the current and future care and well-being of individuals with NMDs. In addition, it offers a platform to observe the overall outcome of patients receiving new drugs and to improve communication and collaboration.

The specific aims of the registry are therefore:

1. Provide epidemiological data:
    a. Incidence
    b. Prevalence
    c. Clinical spectrum at diagnosis
    d. Disease progression / prognosis
    e. Survival rates and mortality
2. Provide a platform for clinical research and post marketing follow-up:
    a. Recruit patients into therapeutic trials
    b. Collection of outcome data during treatment
    c. Facilitate observational studies
       e.g. on healthcare, education and quality of life
3. Provide a platform for communication:
    a. Promote the exchange of knowledge between clinics, researchers, therapists and health authorities
    b. Facilitate national and international collaborations

3.2. Inclusion criteria

The Swiss-Reg-NMD includes children, adolescents and adults living or treated in Switzerland who are diagnosed with a NMD. The diagnosis needs to be confirmed, whenever possible, by genetic testing, or at least by biopsy and/or electroneuromyography, according to international standards for the diagnosis of the given NMD. Once the diagnosis is established, there are no specific exclusion criteria.

Previously, only patients with DMD/BMD and SMA were included in the registry. Since 2018, also patients with a congenital muscular dystrophy (CMD) due to mutations in the laminin-α2 (LAMA2) and collagen VI (COL6) genes are included. In the future, patients with other NMDs may also be included.

Duchenne Muscular Dystrophy (DMD) is an X-linked progressive muscular dystrophy affecting one in every 3’600-10'000 live male births (Mah et al. 2014). Becker Muscular Dystrophy (BMD)

is the less severe form affecting about one in every 18’000 live male births (Emery et al. 1991). Patients with a less severe form than DMD but more severe than BMD are classified as intermediate form (IMD). These disorders are caused by mutations in the dystrophin gene. Boys present delayed motor development and muscle weakness and progress to loss of ambulation, and, in the more severe cases, respiratory and heart failure.

Spinal Muscular Atrophy (SMA) is a disease affecting motor neurons in the spinal cord and the brain stem. It is an autosomal recessive disease affecting about one in every 10'000 live births (Faravelli et al. 2015). It is caused by mutations in the ‘survival motor neuron 1’ gene (SMN1). SMA patients present with progressive motor weakness and weakness of bulbar and respiratory muscles. Conventionally, SMA is divided into four clinical subtypes, from type I with onset before 6 months and, if untreated, death before the second birthday to type IV with adult onset weakness and a slowly progressing course. Recently, the first treatment for SMA, Nusinersen (Spinraza), has been approved by Swissmedic.

Congenital muscular dystrophies (CMD) are a group of diseases that are mostly inherited in an autosomal recessive fashion. The prevalence has been estimated at 7 x 10-6 (Mostacciuolo et al. 1996). LAMA2-related CMD (merosin deficient CMD, or MDC1A) and COL6-related muscular dystrophy are the two most frequent forms of CMD. Both forms lead to marked weakness of skeletal muscles, the tendency to develop contractures and rigidity of the spine as well as respiratory muscle weakness. A phase I trial with Omigapil was conducted in the US and other therapeutic compounds showing promising results in preclinical studies are in development. It is therefore important to include these forms for natural history data and trial readiness.

3.3. How are patients reported

In general, a paediatric or adult neurologists diagnoses an individual with an NMD. The physician then informs the patient and/or their parents (or other legal representative) about the Swiss-Reg-NMD during a routine medical consultation. The physician also gives them printed information about the registry and a form that that they can sign if they want to participate in the registry (informed consent form). This information can be taken home so that a decision taken to be taken after careful deliberation.

In the case of DMD/BMD, most genetic testing is done by the genetic laboratory in Bern. This laboratory also reminds the physicians of the existence of the Swiss-Reg-NMD. This has not yet been implemented for SMA, MCD1A or COL6-related CMD as several laboratories across Switzerland perform the genetic testing for these patients.

If consent is given, the physician reports the patient to the Swiss-Reg-NMD, and provides updates on the clinical status of the patient at regular intervals (once per year or, for SMA, 2-3 times per year for post-marketing follow-up). At the ISPM (the Institute of Social and Preventive

Medicine of the University of Bern where the registry is hosted), this information is then entered into a secured database.

If consent is not given, the patient can still be reported, but with very minimal non-identifying data (diagnosis, gender, birth year, death) to allow a proper estimate of the incidence and prevalence of the diseases in Switzerland to be made. No further information is collected.

3.4. Data protection / Ethics approval

The Human Research Act (HFG) sets the framework conditions for medical research. The Swiss-Reg-NMD is subject to this Act. In 2008, the old registry for DMD/BMD and SMA received ethics approval in the different cantons. In 2018 approval for the new, improved, Swiss-Reg-NMD was obtained from the Cantonal Ethics Committee of Bern. This approval allows the collection of data all over Switzerland. Patients who previously consented to be included in the registry for DMD/BMD and SMA must be asked to provide a new consent for the Swiss-Reg-NMD, as its aims and the use of the data are now broader.

The Swiss-Reg-NMD is now authorised to collect the clinical data on patients as long as these data are collected routinely in the course of the treatment and follow-up of the patient. It is permitted to use these data for reports and in-depth research studies. In addition, the registry is allowed to initiate questionnaire studies on quality of life, development, health and health care use. Finally, the registry can inform patients directly about clinical trials.

Study information and consent forms are available in three different languages (French, German and Italian). All data made available to the Swiss-Reg-NMD is stored in a secure IT environment at the University of Bern. This data is kept strictly in accordance with the requirements of the Data Protection Acts. All staff members of the Swiss-Reg-NMD are bound to professional secrecy. Only coded data (without names or identifying data) is used for research purposes.

4. Organisational structure of the Swiss-Reg-NMD

4.1. General organisation

On a daily basis, the Swiss-Reg-NMD is run by a clinical lead and a small executive office. The registry has a steering group which meets a few times per year. This board is intended to be small and consists of both paediatric neurologists as well as neurologists working across different neuromuscular centres in Switzerland. The overall lead of the registry is shared between the clinical lead and a legal representative at the ISPM. Nine neuromuscular centres report regularly to the registry.

In 2018 the clinical lead of the registry was handed over from Clemens Bloetzer to Andrea Klein, who had been in the steering committee since the registry was founded. Also, towards the end of this year a new coordinator joined the team. From 2019 two new members will strengthen the steering board.

Table 1. People involved in the registry

Lead		
Clemens Bloetzer, MD	Clinical lead until June 2018	CHUV, Lausanne and ISPM, Bern
Andrea Klein, PD MD	Clinical lead from June2018	Inselspital, Bern; UKBB, Basel; CHUV, Lausanne
Claudia Kuehni, Prof. MD	Legal representative	ISPM, Bern
Steering Board		
Andrea Klein, PD MD	Chair, Paediatric Neurologist	Inselspital, Bern; UKBB, Basel; CHUV, Lausanne
David Jacquier, MD	Paediatric Neurologist	CHUV, Lausanne
Paolo Ripellino, MD	Neurologist	EOC, Lugano
From 2019 two further members have been added to the steering board:		
Georg Stettner, PD MD	Paediatric Neurologist	Kinderspital Zürich
Olivier Scheidegger, MD	Neurologist	Inselspital Bern
Executive Office		
Andrea Klein, PD MD	Clinical lead	Inselspital, Bern; UKBB, Basel; CHUV, Lausanne
Claudia Kuehni, Prof. MD	Legal representative	ISPM, University of Bern
Anne Tscherter, PD PhD	Project coordination	ISPM, University of Bern
Michelle Kruijshaar, PhD	Project coordination end ‘18	ISPM, University of Bern
Nadine Lötscher, Nrs	Data manager	ISPM, University of Bern
Advisors		
F. Joncourt, MD	Genetic curator	Previously Genetic Laboratory University Hospital Bern
Participating centres		
Aarau, Basel, Bern, Geneva, Lausanne, Luzern, St. Gallen, Tessin, Zürich, and some private practices.		

4.2. University of Bern

The Swiss-Reg-NMD is hosted at, and legally embedded in, the Institute of Social and Preventive Medicine of the University of Bern.

The address of the registry is:
Swiss-Reg-NMD
Institute of Social and Preventive Medicine
University of Bern
Mittelstrasse 43
CH-3012 Bern
Switzerland
Tel. +41 (0)31 631 33 95
Email: swiss-reg-nmd@hin.ch

4.3. Funding 2018

In 2018 the Swiss-Reg-NMD received unconditional funding from the 'Schweizerische Muskelgesellschaft'; the 'Association Suisse Romande Intervenant contre les Maladies neuro-Musculaires'; the 'Associazione malattie genetiche rare della svizzera italiana', the 'Schweizerische Stiftung für die Erforschung der Muskelkrankheiten' and from PTC Therapeutics. We are very grateful to these organisations for their support.

The funding received in 2018 and the years before has been limited. While it was enough in those years to receive patient reports and fulfil the aim of facilitating the inclusion of patients into trials, more funding will be needed to allow the registry to fulfil its new roles of post-marketing follow-up and providing epidemiological data. Moreover, the work that is needed to adapt the registry in 2019-20 will need additional funding. Chapter 5 details the work that was done in 2018, while Chapter 6 summarizes the next steps that need to be taken.

5. Achievements of the Swiss-Reg-NMD in 2018

5.1. Patients reported

In 2018, a total of 21 new patients with neuromuscular disorders were reported to the registry: eight with SMA, seven with MDC1A and five with DMD/BMD.

The total number of patients that have been reported to the registry since 2008 and have not been reported as deceased is shown in Table 2. A total of 325 patients with neuromuscular disorders are known to live in Switzerland: 177 DMD patients, 51 BMD/IMD patients, and 97 patients with SMA. Patients with MDC1A have not been included in this table because these patients were not reported to the registry until 2018.
To ensure patient confidentiality we mask in our annual report numbers below five with "<5".

Table 2. Total number of patients alive[a], by centre and neuromuscular disorder, Switzerland 2008 – 2018[b].

Centre	DMD	BMD	IMD	SMA1	SMA2	SMA3	SMA4	Total
Aarau	6	<5	0	0	0	<5	0	**9**
Basel	30	5	0	0	<5	<5	0	**40**
Berne	20	<5	<5	<5[c]	7	<5	0	**36**
Geneva	9	<5	0	0	<5	<5	0	**12**
Lausanne	29	13	<5	<5	13	8	0	**66**
Lucerne	6	<5	0	<5	<5	<5	0	**11**
St. Gallen	<5	<5	0	0	<5	12	0	**22**
Tessin	7	9	0	<5	5	0	<5	**23**
Zurich	66	11	<5	<5	13	8	<5	**104**
Total	**177**[d]	**46**	**5**	**10**	**46**	**39**	**<5**	**325**

Numbers below five have been masked to ensure patient confidentiality. DMD: Duchenne Muscular Dystrophy; BMD: Becker Muscular Dystrophy; IMD: Intermediate form; SMA1-4: Spinal Muscular Atrophy type 1-4. [a] Not reported as deceased; [b] Status as at 25-01-2019; [c] Additional patients from other centres are treated with Nusinersen in Bern and seen in two centres. [d] Approximate value to ensure patient confidentiality (St. Gallen DMD and SMA4.

In comparison, annual reports from previous years have shown a larger total number of patients. The reason for this is that these reports showed the number of patients ever reported, including those who have since been reported as deceased. Table 4 shows the total number of patients ever reported to the registry for the last four years. In total 47 patients have been reported as deceased between 2008 and 2018, of whom 5 patients in 2018.

Table 4. Total number of patients ever reported by year, Switzerland 2015-2018.

Year	DMD/BMD/IMD	SMA1-4	Total
2015	239	93	332
2016	255	98	353
2017	258	102	360
2018	264	106	372

DMD: Duchenne Muscular Dystrophy; BMD: Becker Muscular Dystrophy; IMD: Intermediate form; SMA1-4: Spinal Muscular Atrophy type 1-4

The above figures of new and existing patients are likely to be an underestimate of the incidence and prevalence of these diseases in Switzerland as there is likely to be a certain extent of underreporting. Reasons for underreporting include: 1) some patients do not want to participate in the registry; 2) informed consent was not asked for severe cases of SMA 1 who were not treated with Nusinersen and died shortly after diagnosis; 3) since 2017 there has been a delay in asking informed consent as the new consent form only became available in all languages towards the end of 2018. The first source of underreporting should be diminished in the future as the new ethics approval from 2018 allows patients who do not want to participate to be included with minimal non-identifying data.

5.2. Requests for information and inclusion of patients in trials

In 2018, the registry received three requests from companies to assess how many Swiss patients could potentially be recruited for clinical trials. These requests could be addressed swiftly. Due to the new treatment available for SMA as well as other compounds being in development for this disease, we also received requests from pharmaceutical companies, the international alliance TREAT-NMD, and the Bundesamt für Sozialversicherungen (BSV) regarding the numbers of SMA patients. These request were also answered promptly.

Since 2008 around 50 patients have been included in clinical trials in Switzerland and around 10 to 20 have participated in trials abroad.

There are currently two trials involving DMD patients that are conducted in Switzerland: TAMDMD and SIDEROS. TAMDMD is an international placebo controlled trial lead by Prof. Dirk Fischer at the UKBB Basel, investigating Tamoxifen in DMD patients. Screening for this study started in 2018, when 12 Swiss patients were screened. Currently, 9 Swiss patients are included in the trial.

The SIDEROS study is an international study run by Santhera, which investigates the effect of Idebenone on lung function evolution in patients with DMD receiving steroids. Screening and inclusion for this study started in 2017, when 6 patients screened and 5 included at the site in Basel (UKBB, principal investigator PD Andrea Klein). In 2018 a further <5 patients were screened and enrolled at the site in Basel. Thanks to the registry, enrolment into this trial was

very fast. The site in Basel was globally the site that recruited the most patients for many months.

For SMA, three international studies have enrolled Swiss patients in 2018: the “Fish Studies” conducted by Roche. These studies investigate the effect of risdiplam, a small molecule that enhances the functioning of the SMN2 gene, in different groups of SMA patients. “Firefish” is performed in type 1 patients and has a site in Basel (UKBB, principle investigator PD Andrea Klein). “Sunfish” includes patients with SMA type II and III and has no site in Switzerland (patient are sent to Freiburg, Germany). “Jewelfish” is performed in patients who were previously treated with Nusinersen or Olesoxime (in the earlier “Moonfish” trial) and has a site in Basel (UKBB, principle investigator Prof. Dirk Fischer). In total <5 Swiss patients are currently enrolled in the Fish trials.

In addition to these patients, <5 SMA patients are still participating in the SHINE study assessing the long-term safety and tolerability of Nusinersen.

5.3. Collaboration with TREAT-NMD (www.treat-nmd.eu)

TREAT-NMD alliance is an international collaboration of clinicians and researchers in the field of neuromuscular diseases. It also has strategic partnerships with patient organisations and pharmaceutical companies across the world. The aim of TREAT-NMD is to provide an infrastructure to accelerate the development of treatments for NMDs and improve patient care on an international scale. It has built/is building an international patient registry for the different NMDs. TREAT-NMD was born from the European Union Grant funded TREAT-NMD neuromuscular network (2007-2011).

In 2018, we provided the total numbers of patients registered with SMA per type and age-group to Treat-NMD for their overview for their international registry. There was also close communication with TREAT-NMD regarding the medical data to be collected in the clinics for the post-marketing follow-up of SMA patients. Andrea Klein is an elected member of The Global Database Oversight Committee (TGDOC) of TREAT-NMD for the international registry for SMA and DMD.

5.4. Changes made to the registry in 2018

In 2016 it became clear that the registry had to undergo changes in order to assure that it would collect the information needed to address today’s questions in the NMD field and meet current and future data quality and security standards. For this reason, the registry was moved to the ISPM in Bern where there is a centre for childhood disease registries (SwissPedRegistry).

5.4.1 New ethics application

Because of the many changes that were foreseen, the registry needed to reapply for ethics approval in Bern. An extensive document was drafted, and patient information leaflets had to be adapted for different patient groups and in three different languages. In addition the ethics templates ware changed during the application process, which led to further time consuming changes. The first version of the application was returned with questions and an amendment was written and questions answered before final approval was received on 20.06.2018. Chapter 3.4 outlines what our present ethics approval includes.

5.4.2 Re-consenting patients

Because of the new ethics approval, all the patients who previously consented to be included in the Registry for DMD/BMD and SMA have to be asked to consent again based on the new information.

We discussed with our contacts in the participating centres how this could best be arranged. Most of the centres have asked us to contact (part of) their patients directly for this. Before this could be done information was exchanged with the centres to ensure that addresses were up to date and that there were no reasons why patients should not be approached. So far, we obtained the new consent of about one third of those previously included.

5.4.3 Defining which data (variables) will be collected

Given the recent changes in the field of neuromuscular disorders, the medical data (variables) that we ask the clinics to report to the registry needed to be checked, updated and clearly defined. Also, the registry previously did not use a case report form (CRF), but extracted data from clinical reports. This meant that data was sometimes incomplete, as often some variables were not mentioned in the clinical report, or reported in a non-standard format.

During 2017-2018 TREAT-NMD was preparing recommendations on which variables should be collected internationally for the post-marketing follow-up of SMA patients. Based on a draft version of these recommendations and our own experiences with the data we collected previously, a test version of the CRF for Swiss SMA patients was generated and distributed amongst the participating clinicians. The CRF for SMA will be finalized in the first half of 2019, based on discussions with the steering board, feedback from clinicians, and taking into account the final version of the TREAT-NMD recommendations.

During 2018 the reporting of DMD/BMD patients continued as before without a CRF. TREAT-NMD had defined a dataset for DMD a few years ago, which have been collected in the Swiss registry since 2008. We compared the list of variables that we used to collect in the Swiss registry to the dataset of the UK NorthStar Neuromuscular Clinical Network, to ensure international comparability. Based on this comparison, a draft list of variables was prepared by the executive board to start discussions with the steering board in January 2019.

5.4.4 Fundraising

During the second half of 2018 more effort has gone into fundraising than in previous years because of the expected additional workload to finish improving the registry. We have had discussions with a pharmaceutical company, Biogen, to fund a large amount of work over a 3-year period. We hope these discussions will be successful. In addition, PTC therapeutics has committed to fund us again in 2019 with an unconditional grant.

5.4.5 Organisation

In 2018 a start was made to further formalize the organisational structure of the registry. A small steering board was set-up. A dedicated data manager was appointed in 2017 for 1 day a week, as well as a coordinator for half a day per week.

5.4.6 Dissemination

In 2018, a website was created for the registry: www.swiss-reg-nmd.ch. This website contains brief information about the registry. The information leaflets and consent forms can also be downloaded from the website.

The registry was represented in the following meetings in 2018:

- Meeting of the medical advisory board of Myosuisse, Zürich 23.8.18 (AK)
- SMA day, Nottwil 25.8.18 (AK)
- SMA meeting with paediatric and adult neurologists, Zürich 4.9.18 (AK, AT)
- Swiss Duchenne Conference, Nottwil 7-8.9.18 (AK)
- Annual meeting of the Swiss Society of Pediatric Neurology, Geneva 4./15.11.18 (AK)

5.4.7 Research

During 2018 the first questionnaire study to assess education, leisure activities and quality of life in young patients with DMD in Switzerland was initiated. Questionnaires and information leaflets were prepared by a Master student (Sarah Erni). The study will now have to be announced to the Cantonal Ethics Committee of Bern after which children aged 8-18 who are known in the registry as having DMD will be sent this questionnaire.

6 Next steps

The main goal of the Swiss-Reg-NMD for 2019 is to continue making the improvements to the registry to make it fit for present and future needs. We need to continue the re- consenting of patients and finalize the list of variables that is to be collected for each disease. In addition to this, a major piece of work for 2019 is to develop a new database for the registry and to transfer all the previously collected data into this database.

This work is in addition to the standard work that the registry has to do each year. This routine work includes collecting clinical information on patients, consenting new patients, identifying patients for trials, and disseminating information, as well as fundraising and administration.

In the longer-term, once the registry is fully functional, it is envisioned that the registry not only facilitates participation of patients in trials, but also provides basic epidemiological, outcome data for public health purposes, as well as data for research. This means that there will be more information to analyse and also most likely more information requests to come our way. Guidelines need to be developed describing what information we can and cannot provide and the relevant remuneration.

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