Swiss-Reg-NMD

UNIVERSITÄT BERN

Swiss Registry for Neuromuscular Disorders

Annual report for 2019

Swiss-Reg-NMD

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1. Executive Summary

The 'Swiss registry for neuromuscular disorders' (Swiss-Reg-NMD) collects medical information from people with neuromuscular disorders. It is led by specialized physicians from all over Switzerland and located at the Institute of Social and Preventive Medicine (ISPM) in Bern. The registry includes children and adults living in Switzerland who are diagnosed with Duchenne-Becker Muscular Dystrophy (DMD/BMD), Spinal Muscular Atrophy (SMA) and recently also merosin-deficient muscular dystrophy also called *LAMA2*-related muscular dystrophy (MDC1A respectively LAMA2).

The Swiss-Reg-NMD pursues the following objectives:

- to register and to collect relevant health data of any patient affected by a neuromuscular disorder living in Switzerland
- to facilitate the participation of patients in National and International therapeutic trials
- to facilitate the establishment of study centers in Switzerland
- to harmonize diagnosis and care on a national level (standards of care)
- to establish a national platform for Post-Marketing Surveillance

The registry recently moved to the ISPM in Bern and was modernized to meet current and future data quality and security standards and satisfy the needs of patient organisations, health authorities and research organisations. The registry operates now according to the new ethics approval (20.06.2018).

In 2019, we have put a lot of effort into obtaining the re-consent from the formerly included patients. We have now excluded previously registered patients, which we could not track and ask for re-consent. On 31.12.2019, a total of 247 patients with neuromuscular disorders were registered in Swiss-Reg-NMD (not reported as deceased): 161 patients are affected by a dystrophin associated muscular dystrophy (DMD/BMD/IMD), 79 patients by SMA and 7 patients by LAMA2.

As in previous years, the registry answered requests from multiple stakeholders, in 2019 we answered: 1) from companies to assess the potential of recruiting patients for a clinical trial, 2) from investigators in university hospitals on the feasibility of clinical studies and 3) from the Federal Social Insurance Office on the effectiveness of drugs. In 2019, 11 DMD patients participated in the TAMDMD study and 6 DMD patients in the SIDEROS study. In 2019, <5 SMA patients participated in the Jewelfish trial, <5 SMA patients in the SHINE study and <5 SMA Swiss patients participated in a gene therapy study abroad.

In addition to facilitating the inclusion of patients into trials, the registry aims to assess the effectiveness and side effects of new drugs after their marketing approval. We also want to learn more on the health, care and needs of people with an NMD in Switzerland. This requires the collection of clearly defined medical data. In 2019, we have finalized the definition of the medical data that we collect from SMA patients and the development of a new secure database. We have almost finished this work also for DMD/BMD.

In 2019 the Swiss-Reg-NMD received funding from 'Schweizerische Muskelgesellschaft', 'Association Suisse Romande Intervenant contre les Maladies neuro-Musculaires', 'Associazione malattie genetiche rare della svizzera italiana','SMA Schweiz', Biogen Switzerland, Roche Pharma Schweiz, Avexis EU, PTC Pharmaceuticals and the 'Schweizerische Stiftung für die Erforschung der Muskelkrankheiten'. We thank these organisations for their support.

Zusammenfassung

Das 'Schweizer Register für neuromuskuläre Erkrankungen' (Swiss-Reg-NMD) sammelt medizinische Informationen von Menschen mit neuromuskulären Erkrankungen. Es wird von Fachärzten aus der ganzen Schweiz geführt und ist am Institut für Sozial- und Präventivmedizin (ISPM) in Bern angesiedelt. Das Register erfasst Kinder und Erwachsene, die in der Schweiz leben und bei denen Duchenne-Becker-Muskeldystrophie (DMD/BMD), Spinale Muskelatrophie (SMA) und seit kurzem auch Merosin-negative Muskeldystrophie, auch LAMA2-assozierte Muskeldystrophie (MDC1A bzw. LAMA2) genannt, diagnostiziert wurde.

Das Swiss-Reg-NMD verfolgt die folgenden Ziele:

- die Registrierung und Erfassung relevanter Gesundheitsdaten aller in der Schweiz lebenden Patienten mit neuromuskulären Erkrankungen
- die erleichterte Teilnahme von Patienten an nationalen und internationalen therapeutischen Studien
- die erleichterte Einrichtung von Studienzentren in der Schweiz
- die Harmonisierung von Diagnose und Versorgung auf nationaler Ebene (Versorgungsstandards)
- die Einrichtung einer nationalen Plattform für die Post-Marketing-Überwachung

Das Register ist vor kurzem ans ISPM in Bern umgezogen und wurde modernisiert, um die aktuellen und zukünftigen Datenqualitäts- und Sicherheitsstandards zu erfüllen und den Bedürfnissen von Patienten-organisationen, Gesundheitsbehörden und Forschungsorganisationen gerecht zu werden. Das Register arbeitet nun gemäss der neuen Ethik-Genehmigung (20.06.2018).

Im Jahr 2019 haben wir viel Mühe darauf verwendet, die erneute Einwilligungserklärung der ehemals eingeschlossenen Patienten einzuholen. Wir haben nun zuvor registrierte Patienten ausgeschlossen, die wir nicht erreichen und um eine erneute Einwilligung bitten konnten. Am 31.12.2019 waren insgesamt 247 Patienten mit neuromuskulären Erkrankungen im Swiss-Reg-NMD registriert (nicht als verstorben gemeldet): 161 Patienten mit einer Dystrophin assoziierten muskulären Dystrophie (DMD/BMD/IMD), 79 Patienten mit SMA und 7 LAMA2-Patienten.

Wie in den vergangenen Jahren beantwortete das Register im 2019 Anfragen von mehreren Interessengruppen: 1) von Unternehmen, um das Potenzial der Rekrutierung von Patienten für eine klinische Studie zu prüfen, 2) von Universitätskliniken zur Durchführbarkeit klinischer Studien und 3) vom Bundesamt für Sozialversicherung zur Wirksamkeit von Medikamenten. In 2019 nahmen 11 DMD-Patienten an der TAMDMD-Studie und 6 DMD-Patienten an der SIDEROS-Studie, <5 SMA-Patienten an der Jewelfish Studie, <5 SMA-Patienten an der SHINE-Studie und <5 Schweizer SMA-Patienten an einer Gentherapie-Studie im Ausland teil.

Neben der Erleichterung des Einschlusses von Patienten in die Studien soll das Register auch Daten zur Wirksamkeit und die Nebenwirkungen neuer Medikamente nach deren Marktzulassung erfassen. Wir wollen auch mehr über die Gesundheit, die Versorgung und die Bedürfnisse von Menschen mit einer NME in der Schweiz erfahren. Dies erfordert eine Erhebung klar definierter medizinischer Daten. Im Jahr 2019 haben wir die Definition der medizinischen Daten, die wir von SMA-Patienten sammeln, und die Entwicklung einer neuen sicheren Datenbank abgeschlossen. Auch für die DMD/BMD Daten haben wir diese Arbeit nun fast beendet.

Im Jahr 2019 erhielt die Swiss-Reg-NMD finanzielle Unterstützung von der Schweizerischen Muskelgesellschaft, der Association Suisse Romande Intervenant contre les Maladies neuro-Musculaires, der Associazione malattie genetiche rare della svizzera italiana, der SMA Schweiz, Biogen Schweiz, Roche Pharma Schweiz, Avexis EU, PTC Pharmaceuticals und der Schweizerischen Stiftung für die Erforschung der Muskelkrankheiten. Wir danken diesen Organisationen für ihre Unterstützung.

Sommaire

Le «registre suisse des maladies neuromusculaires» (Swiss-Reg-NMD) recueille des informations médicales de personnes atteintes d'une maladie neuromusculaire. Il est dirigé par des médecins spécialistes de toute la Suisse et se trouve à l'Institut de médecine sociale et préventive (ISPM) à Berne. Le registre inclut des enfants et des adultes vivant en Suisse avec un diagnostic de dystrophie musculaire de Duchenne-Becker (DMD/BMD), d'amyotrophie spinale (SMA) et, plus récemment, de dystrophie musculaire mérosine-négative ou dystrophie musculaire liée à *LAMA2* (anciennement MDC1A, ici LAMA2).

Le Swiss-Reg-NMD poursuit les objectifs suivants :

- enregistrer et collecter les données médicales essentielles de tout patient atteint d'une maladie neuromusculaire vivant en Suisse
- faciliter la participation des patients dans des études cliniques thérapeutiques nationales et internationales
- faciliter la création de sites d'étude clinique en Suisse
- harmoniser le diagnostic et les soins au niveau national (standards de soins)
- mise en place d'une plate-forme nationale pour la surveillance post-commercialisation

Le registre a récemment été transféré à l'ISPM à Berne et a été modernisé pour répondre aux normes actuelles et futures de qualité et de sécurité des données et pour satisfaire aux besoins des associations de patients, des autorités de santé et des organismes de recherche. Le registre fonctionne désormais conformément à la nouvelle approbation éthique (20.06.2018).

En 2019, nous nous sommes employés à obtenir le nouveau consentement des patients précédemment inclus. Nous avons maintenant exclu les patients précédemment inclus que nous n'avons pas réussi à contacter pour demander un nouveau consentement. Au 31.12.2019, un total de 247 patients atteints de maladies neuromusculaires étaient enregistrés dans le Swiss-Reg-NMD (non déclarés comme décédés): 161 patients sont atteints d'une dystrophie musculaire (DMD/BMD/IMD), 79 patients d'une SMA et 7 patients de LAMA2.

Comme les années précédentes, le registre a répondu en 2019 aux demandes de multiples acteurs : 1) des entreprises pour évaluer le potentiel de recrutement de patients pour un essai clinique, 2) des chercheurs des hôpitaux universitaires sur la faisabilité des études cliniques et 3) de l'Office fédéral des assurances sociales sur l'efficacité des médicaments. En 2019, 11 patients atteints de DMD ont participé à l'étude TAMDMD et 6 patients atteints de DMD ont participé à l'étude SIDEROS. En 2019, <5 patients SMA ont participé à l'étude Jewelfish, <5 patients SMA à l'étude SHINE et <5 patients SMA suisses ont participé à une étude de thérapie génique à l'étranger.

En plus de faciliter l'inclusion de patients dans les essais cliniques, le registre vise à évaluer l'efficacité et les effets secondaires des nouveaux médicaments après leur autorisation de mise sur le marché. Nous voulons également en savoir plus sur la santé, les soins et les besoins des personnes atteintes d'une NMD en Suisse. Cela nécessite la collecte de données médicales clairement définies. En 2019, nous avons finalisé la définition des données médicales que nous recueillons auprès des patients atteints de SMA et le développement d'une nouvelle base de données sécurisée. Nous avons presque terminé ce travail également pour la DMD/BMD.

En 2019, 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 'SMA Schweiz', Biogen Suisse, Roche Pharma Suisse, Avexis EU, PTC Pharmaceuticals et de 'Schweizerischen Stiftung für die Erforschung der Muskelkrankheiten'. Nous tenons à remercier ces organisations pour leur soutien.

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.

In 2008, a national registry for NMD was launched at the Centre hospitalier universitaire vaudois (CHUV) in Lausanne to give patients access to new therapies and to facilitate the identification of patients for clinical trials in Switzerland. In 2017, the registry moved to the Institute of Social and Preventive Medicine (ISPM) in Bern and was modernized to meet current and future data quality and security standards and satisfy the needs of patient organisations, health authorities and research organisations. Its long-term goal is to improve the care and well-being of people with neuromuscular diseases in Switzerland.

This report provides an overview of the Swiss-Reg-NMD and its activities in 2019.

3. Description of the Swiss-Reg-NMD

3.1. Organisational structure

On a daily basis, the Swiss-Reg-NMD is run by a clinical lead and an 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. The organisational structure of the Swiss-Reg-NMD is displayed in Table 1.

Table 1. People involved in the registry

Lead		
Andrea Klein, PD MD	Clinical lead	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	Paediatrician	CHUV, Lausanne
Paolo Ripellino, MD	Neurologist	EOC, Lugano
Georg Stettner, PD MD	Paediatric Neurologist	Kinderspital, Zürich
Olivier Scheidegger, MD	Neurologist	Inselspital, Bern
Executive Office		
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 to end ‘19	ISPM, University of Bern
Dominique Baumann, PhD	Project coordination	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.		

3.2. 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. Recruitment of patients into therapeutic trials
    b. Collection of outcome data during treatment
    c. Facilitation of observational studies
    e.g. on healthcare, education and quality of life
3. Provide a platform for communication:
    a. Promotion of the exchange of knowledge between clinics, researchers, therapists and health authorities
    b. Facilitation of national and international collaborations

3.3. 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.

Currently, patients with DMD/BMD/IMD, SMA and patients with a congenital muscular dystrophy (CMD) due to mutations in the laminin-α-2 gene (LAMA2 also named MDC1A) or collagen VI (COL6) genes are included in the registry. 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 7×10^{-6} (Mostacciuolo et al. 1996). LAMA2-related muscular dystrophy 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 study 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.

3.4. Registration of patients and collection of medical data

In general, a paediatric or adult neurologist diagnoses an individual with a 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 they can sign if they want to participate in the registry (informed consent form). This information can be taken home so that a decision can be made after careful deliberation.

If consent is given, the physician reports the patient to the Swiss-Reg-NMD, and provides data 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.

3.5. 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.

If consent is given, the Swiss-Reg-NMD is authorised to collect the medical data 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 four different languages (French, German, Italian and English). 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.

3.6. Funding

During 2019, huge effort has gone into fundraising, because of the additional workload to finish the improvement of the registry.

In 2019, the Swiss-Reg-NMD has 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', from 'SMA Schweiz' and the 'Schweizerische Stiftung für die Erforschung der Muskelkrankheiten'.
Furthermore, Roche Pharma Schweiz AG and PTC Pharmaceuticals have supported the work of the Swiss-Reg-NMD with an unconditional grant. Avexis EU Limited has also financially supported the registry in 2019, with the condition that they receive an activity report. On August 2019, an important sponsored research agreement between Biogen Switzerland AG and the Institute of Social and Preventive Medicine could be made. The registry regularly provides a report to Biogen Switzerland AG containing summarized information. None of these reports contain information that allow the identifications of single patients.

We are very grateful to all these organisations for their support.

4. Registered cases

The registry operates now according to the new ethics approval (20.06.2018). Therefore, we have excluded all previously registered patients, which could no longer be tracked and ask for re-consent.
On 31.12.2019, a total of 247 patients with neuromuscular disorders were registered in Swiss-Reg-NMD (not reported as deceased): 130 DMD patients, <35 BMD/IMD patients, 79 patients with SMA, and <10 patients with LAMA2-related muscular dystrophy.
In 2019, <5 SMA I and <5 DMD patients included in the Swiss-Reg-NMD were reported as deceased.
To ensure patient confidentiality we mask small numbers with "<5" or "<10" in our annual report.

Table 2. Total number of patients alive[a], by centre and neuromuscular disorder, Switzerland (status as at 31.12.2019).

Centre	DMD	BMD	IMD	SMA1	SMA2	SMA3	LAMA2	Total
Aarau	6	<5	0	0	0	<5	0	**<10**
Basel	27	<5	0	0	<5	<5	<10	**39**
Berne	13	0	<5	<5[b]	6	<5	0	**27**
Geneva	<5	0	0				<10	**<10**
Lausanne	25	9	<5				0	**<40**
HUG+ CHUV[c]				<5	12	<5		**17**
Lucerne	<5	<5	0	0	<5	<5	0	**8**
St. Gallen	<5	<5	0	<5	<5	9	0	**19**
Ticino	<5	7	0	<5	<5	0	0	**17**
Zurich	44	6	<5	<5	14	6	0	**75**
Total	**130[d]**	**28[d]**	**<5**	**13**	**42**	**24**	**<10**	**247**

Numbers below five and ten have been masked to ensure patient confidentiality. DMD: Duchenne Muscular Dystrophy; BMD: Becker Muscular Dystrophy; IMD: Intermediate form; SMA1-3: Spinal Muscular Atrophy type 1-3; LAMA2: *LAMA2*-related muscular dystrophy.
[a] Not reported as deceased; [b] Additional patients from other centres are treated with Nusinersen in Bern and seen in two centres; [c] Geneva and Lausanne share the treatment of many SMA patients;
[d] Approximate value to ensure patient confidentiality

Not all patients with a NMD living or treated in Switzerland are registered in the Swiss-Reg-NMD. The participation is voluntary and some patients do not want to participate in the registry. In addition, in 2018 and 2019, our focus was on the modernization of the registry, and not on the promotion of registration of all patients.

5. Achievements of the Swiss-Reg-NMD in 2019

5.1. Requests to the registry

The registry always replies to requests in a way that no identifying information is disclosed. Conclusions about individual persons are not possible under any circumstances.

Requests on the feasibility for studies and recruitment for clinical trials

- We have responded to a request from a Swiss university hospital to provide information on potential SMA patients eligible for an observational study.
- We have answered a request from TREAT-NMD on behalf of a pharmaceutical company. We have provided aggregated information about DMD patients who are eligible for a possible therapeutic trial.
- We responded to a request from a Swiss university hospital by identifying SMA patients who may be invited to participate in a study to develop a tool to improve monitoring of disease progression.

Further requests

- We have provided information to a pharmaceutical company about the number of untreated SMA patients with a specific age range.
- We have answered a request from a pharmaceutical company by indicating the number of DMD patients with a specific genetic background.
- We have answered a request from a pharmaceutical company wishing to know the current number of DMD patients living in Switzerland by sending them the Annual Report 2018.
- We have answered a request form the BAG on what kind of data are collected for SMA patients.
- At the end of 2019, we took part in a survey conducted by the 'Bundesamt für Gesundheit (BAG)' about the current practice and the challenges of data sharing and record linkage in Switzerland (e,g, on the consent form, the data sources, the use of the data and the aims of the registry).
- We have answered a request for the preparation of the National Health Report 2020 on "Chronic Diseases and Disabilities in Children and Adolescents" regarding the incidence and prevalence of DMD/BMD and SMA in Switzerland.

Post-marketing follow-up

We have completed a detailed report for the Federal Social Insurance Office (FSIO) by the end of October 2019, which provides information for assessing the effectiveness of Nusinersen in treating SMA patients.

We reported on:

- General part: Number of SMA patients by SMA type, treated vs. not treated with Nusinersen and by age group (< 20 and >20 years old).
- Patients treated with Nusinersen: chronological course of motor milestones (e.g. head control, sitting, standing and walking abilities, function of hands) and chronological course of motor assessments (e.g. CHOP-intend, HINE, RULM, HFMS/HFMSE).

This report was made specifically for the responsible officials at the FSIO and is strictly confidential and as such has been sent to the recipient. It contains no information that would allow the identifications of single patients.

5.2. Promotion of national centres and inclusions in clinical trials

There are currently two trials involving DMD patients that are conducted in Switzerland:

- 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 15 Swiss patients were screened. In 2019, another 6 Swiss patients were screened. Currently, 11 Swiss patients are enrolled 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 were screened and 5 included at the site in Basel (UKBB, principal investigator PD Andrea Klein). In 2019, further <5 patients were screened and <5 enrolled at the site in Basel.

There are currently three trials involving SMA patients from Switzerland:

- The Jewelfish trial conducted by Roche investigates the effect of Risdiplam, a small molecule that enhances the functioning of the SMN2 gene, in different groups of SMA patients. In 2019, <5 new Swiss patients have been enrolled. In total, <5 patients participated in 2019 in this trial (UKBB, principle investigator Prof. Dirk Fischer).
- The Sunfish trial conducted by Roche investigates the effect of Risdiplam in comparison with a placebo group in SMA 2 and 3 patients. <5 Swiss patients are included.
- The SHINE study assesses the long-term safety and tolerability of Nusinersen. <5 Swiss SMA patients are currently participating this study.
- <5 SMA Swiss patients are participating in a gene therapy study abroad.

Note: the above mentioned numbers include only the patients registered in Swiss-Reg-NMD.

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

TREAT-NMD is a network for the neuromuscular field that provides an infrastructure to ensure that the most promising new therapies reach patients as quickly as possible. Since its launch in January 2007 the network's focus has been on the development of tools that industry, clinicians and scientists need to bring novel therapeutic approaches through preclinical development and into the clinic, and on establishing best-practice care for neuromuscular patients worldwide.
Dr. Andrea Klein is an elected member of the TREAT-NMD Global Database Oversight Committee (TGDOC) for the international registry for SMA and DMD. The TGDOC is responsible for reviewing all requests for data from the global database.

Collaboration with TREAT-NMD has taken place in 2019 as follows:

- We have provided the aggregated number of SMA patients by SMA type recorded in the registry. This led to a co-authorship of the registry in the poster publication displayed at the CureSMA conference in June 2019, Anaheim (USA): Rodrigues et al; Collaborative data collection by TREAT-NMD Registries to support post-marketing surveillance in Spinal Muscular Atrophy.
- We have provided information about which items the registry collects in the expanded SMA dataset and provided aggregated SMA patients data collected in both the old core and the expanded core dataset. This led to a co-authorship of the registry in the poster publication displayed at the TREAT-NMD conference in December 2019, Leiden (NL): Rodrigues et al; Collaborative data collection by TREAT-NMD Registries to support post-marketing surveillance in Spinal Muscular Atrophy.
- Dr. Andrea Klein, as a member of the TGDOC, has given her vote on several requests for data from the global database.

5.4. Development of the registry

Re-consenting patients

Because of the new ethics approval (20.06.2018), patients who previously consented to be included in the registry for DMD/BMD and SMA from 2008 had to consent again for the Swiss-Reg-NMD.
We have put a lot of effort into obtaining the re-consent from the formerly included patients. In about half the cases, the physicians informed the families about the Swiss-Reg-NMD and collected the new informed consents. In the remaining cases, we informed the families by letter and asked them to send us back the signed informed consent. This process is now almost accomplished. Some of the previously registered patients could no longer be tracked and contacted (lost to follow-up).

SMA: Defining the data set and developing the database

We have revised the selection and definition of the medical data (SMA variables) that we collect in the registry from SMA patients. Accordingly, we have updated the SMA case report form (CRF). It now contains most of the variables suggested by TREAT-NMD, and a few additional ones, selected by the steering board of the registry.

Up to now, we had no structured database that included all the patients and allowed an efficient analysis of the data. Therefore, we developed a new database using REDCap. The database is now fully functional. We can reliably enter all received medical data and export them for analysis.

The setup of this database included the following work steps:

- Implement all variables in the REDCap database
- Organize the variables in so-called instruments according to the sections in the CRF
- Set up a structure that enables longitudinal data collection
- Test the database: enter real life data of 10 patients
- Identify emerging ambiguities and problems and adapt both the database and CRF
- Establish guidelines that regulate the handling of the new database
- Set the database to production
- Train the data manager for the data entry

DMD/BMD: Defining the data set and developing the database

During 2019 the reporting of medical data from DMD/BMD patients continued as before with medical reports (without a CRF). We have revised the selection and definition of the medical data that we collect in the registry from DMD/BMD patients. We have now developed CRFs also for DMD/BMD and, same as for SMA, built-up a new database (REDCap). This database is now being tested and will be fully functional in spring 2020.

Next steps in 2020

We will implement the following in 2020:

- Consent and data collection from adult patients. We will place a focus on the registration of adult patients and on the collection of their medical data.
- DMD/BMD: Entering the medical data into the database. The DMD/BMD database will be fully functional in spring 2020, therefore we will enter all the so far collected medical data from the medical reports and the newly incoming data from the recently generated CRFs.
- LAMA2: Finalising the data set and developing the database. Like for SMA and DMD/BMD, we will define the medical data that we will collect in the registry from patients affected by LAMA2 related muscular dystrophy. We will develop LAMA2 CRFs and accordingly build-up a new database (REDCap).

5.5. Dissemination

Information about the registry is always available on our website 'www.swiss-reg-nmd.ch', where also the information leaflets and consent forms can be downloaded.

The registry was represented in the following meetings in 2019:

- Internationaler Tag der Seltenen Krankheiten in der Schweiz, 02.03.2019, Basel, (AT, CK)
- Presentation of the Swiss-Reg-NMD at the 'Präsidenten-Treffen', Myosuisse, 20.03.2019, Zürich, (AT)
- Informationsanlass Nationales Konzept Seltene Krankheiten, Bundesamt für Gesundheit, 17. 05.2019, Bern, (AT)
- Meeting of the 'fachlicher Beirat Muskelgesellschaft und Myosuisse', 29.08.2019, Bern, (AK, AT, DB)
- Gemeinsame Jahrestagung der Schweizerischen Gesellschaft für Neuropädiatrie (SGNP) und der Swiss Academy of Childhood Disability (SACD), 13.-14.11.2019, Aarau, (AK, GS, DJ, AT)
- International Conference on MDC1A (LAMA2), November 2019, Maastricht (NL), (AK)
- SGNP, 'Kletterkurs: Neuromuscular Diseases', 23.11.2019, CHUV, Lausanne, (AK, DJ, DB)
- TREAT- NMD Conference, 09.-11.12.2019, Leiden (NL), (AK, MK)

AK Andrea Klein, AT Anne Tscherter, CK Claudia Kuehni, DB Dominique Baumann, DJ David Jacquier, GS Georg Stettner, MK Michelle Kruijshaar

5.6. Research

- The first questionnaire study to assess education, leisure activities and quality of life in young patients with DMD in Switzerland was initiated in 2018. The study has been approved by the Cantonal Ethics Committee of Bern in 2019. This questionnaire will be sent to children aged 8-18, who are known in the registry as having DMD.
- The detailed report for the Federal Social Insurance Office (FSIO), which provides information for assessing the effectiveness of Nusinersen in treating SMA patients, serves as a basis for a scientific publication of the Swiss SMA Data.
- The CRF for LAMA2 patients is being finalised with international collaboration to ensure that natural history data from different countries can be combined to enable the design and recruitment for future trials.

Poster publications

- CureSMA conference in June 2019, Anaheim (USA): Rodrigues et al; Collaborative data collection by TREAT-NMD Registries to support post-marketing surveillance in Spinal Muscular Atrophy (Focus on data collection in registries).
- TREAT-NMD conference in December 2019, Leiden (NL): Rodrigues et al; Collaborative data collection by TREAT-NMD Registries to support post-marketing surveillance in Spinal Muscular Atrophy (Focus SMA medical data).

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