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Registry

Development of an academic disease registry for spinal muscular atrophy

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Abstract

We report the development of a new disease registry on SMA as the result of a collaboration among three national networks in United States, Italy, and United Kingdom in partnership with a biotechnology company and with the support of advocacy groups.

The aim of establishing a large collaborative registry within academic centers was to establish a structured but flexible system for collection of prospective, highly curated data that will deeply phenotype all patients with SMA and follow them longitudinally over several years.

This paper describes the process leading to the development of the registry including the identification of the relevant data elements, the design of an electronic CRF with a shared data dictionary, the piloting of the first version and the definition of the final version.

The registry will provide a central structure for conducting academic studies based on a much larger cohort of patients than those available in the individual networks. Due to the quality control of the data collected the registry can also be used for postmarketing purposes, allowing to share, in a transparent and controlled way, real-world data with pharmaceutical partners, drug regulatory agencies, and advocacy groups for better understanding of safety and effectiveness of new treatments.

Keywords: Disease registry; Spinal muscular atrophy; Neuromuscular disorders.

1. Introduction

Spinal muscular atrophy (SMA) is a severe neuromuscular disease characterized by degeneration of the spinal alpha motor neurons, resulting in progressive proximal muscle atrophy and weakness [1]. In the last few years, new standards of care recommendations have become available [2,3]. Following a number of successful clinical trials [4–6] and the recent approval of effective therapeutic approaches, there is an increasing need for accurate and reliable registries to record the evolving natural history–concentrating on the impact of these evolving standards on disease, the evolution of care, and the short and long term impact of these novel therapies. So far, there have been mainly two approaches to registries for SMA. The great majority are patient-driven registries, often coordinated by advocacy groups, where patients or their families are asked to sign a consent and are responsible for data entry. These registries have the advantage that they can potentially reach a very large number of patients, including some that may not be followed in tertiary care centers. These efforts have been extremely useful to provide epidemiological data on very large cohorts of all types of SMA patients and can capture other important information regarding the levels of care in different countries [7]. The disadvantage of this approach is that there may be a selection

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bias towards patients and their caregivers who are more motivated to participate, the uncurated data are often inserted by patients/carers, and there is no oversight on the accuracy of the data. More accurate data can be obtained by the academic registries and natural history studies of functional measures [8–10]. These have the advantage that they are designed as observational studies, including training of the observers and data monitoring, but have the disadvantage that the data collected reflect a tertiary care setting and not necessarily the whole 'real world' SMA population. In these registries the focus has been largely on functional changes, with relatively less attention to medical details such as adverse events, individual burden of disease/quality of life, or specific health related issues.

Due to the high costs of the new therapies and the ongoing debate on their affordability and their long term efficacy by the different national health systems [11–14], it has become increasingly important to have additional information on hospitalizations and on the overall economic burden of the disease to society and of the impact on the health system in both treated and untreated patients. Consequently, there has been the need to shift from data registries focused on the collection of functional outcome measures to more complex disease registries that would provide accurate and reliable information on natural history and supportive care, hospitalization, potential drug adverse events, and other health-related issues that are relevant for understanding disease impact and treatment impact at both the patient and societal level. In addition, the recent European Medicines Agency (EMA) initiative for patient registries (https://www.ema.europa.eu/en/documents/other/initiative-patient-registries-strategy-pilot-phase_en.pdf) seeks to utilize data from existing disease registries for traditional regulatory purposes including the evaluation of new medicines for safety and effectiveness.

In order to address these aspects, we recently developed a new disease registry network as part of a large international academic collaboration, in partnership with advocacy groups and a biotechnology company and based on existing research networks. The overarching aim of establishing this collaborative registry within academic centers was to establish a flexible system for the accumulation of prospective, highly curated data that will deeply phenotype patients living with SMA – from presymptomatic babies to adults – and follow these patients longitudinally over several years. This registry will serve two main purposes: to function as a central structure for conducting future academic investigations, and to collect and share real-world data with pharmaceutical partners, drug regulatory agencies, and advocacy groups for better understanding of treated phenotypes of SMA as well the real world safety and effectiveness of new treatments.

2. Materials and methods

The development of the new registry of the international Spinal Muscular Atrophy consortium (iSMAc), a prospective cohort study entitled ISMAR (International SMA Registry), is the result of an ongoing collaboration among three large national networks in United States, Italy, and United Kingdom in partnership with a biotechnology company (Biogen) and with the support of advocacy groups. Each network identified one main principal investigator and at least one clinical evaluator (physical therapist) to represent that network in the iSMAC discussions.

Table 1
Subdivision of the process leading to the final registry in 3 principal phases.

Identification of data elements
1) Review of the existing CRFs and data collection forms available in each network
2) Selection of relevant data elements to be included form the existing CRFs
3) Identification of additional data elements
4) Comparing items exploring similar fields
5) Sharing the first version of the new CRF with advocacy groups and industries representatives
Building up an eCRF
6) Simplifying the level of responses to increase accuracy
7) Data dictionary
Pilot version and defining the final version
8) Piloting the first version
9) Data collection

The development of a common registry and of a shared electronic case report form (eCRF) followed different steps, which can be broadly categorized, into 3 sections:

(i) Identification of the relevant data elements; (ii) designing an eCRF with a shared data dictionary; (iii) Piloting the first version and defining the final version.

Table 1 provides details of the process leading to the final registry.

1) *Review of the existing CRFs available in each network*
2) *Identification of relevant data elements to be included*

Each of the participating networks was already curating registries for SMA, with forms capturing functional scales and other aspects of the disease, including demographics and some aspects related to different aspects of care (respiratory, physical therapy, etc.). Each network was already using a form designed for baseline assessment and a different one for follow up. The first form, to be filled at the time of the first observation, with details on genetic diagnosis and past clinical and family history; The second one, to be filled at each follow up visits, including the interval past history and the new assessments; The third form is designed to add retrospective data that can be filled after consent is obtained.

The three forms were carefully scrutinized. Each data element in the three forms was scored as: (a) relevant, (b) potentially useful; (c) not relevant. This exercise was needed as the number of data elements in each scale was very large and also included exploratory fields not currently relevant. The scoring was performed in each of the three networks separately and blindly and the results were discussed, reaching a consensus on the number of existing data elements considered as relevant.

3) *Identification of additional data elements*

Each network was first asked to define if there were additional aspects that were collected as part of the clinical routine that should be more systematically collected using a structured field and a defined set of responses. The list of possible additional items was shared among the 3 networks trying to find consensus on which fields should be added. All networks identified as a priority to add fields reporting accurate details of admissions, severity and duration of respiratory complications and other events requiring a specialist assessment, and a more structured recording of possible concurrent diseases and medications. It was also felt by all the networks that more detailed information on standards of care and access to physiotherapy should be systematically recorded. This information was always available from clinical notes but not previously recorded in a structured format.

The second question was related to the need to add new fields or to add other exams that were not part of the clinical routine. While there were a few suggestions on a number of exams that would have interesting for scientific or exploratory purposes, it was agreed that these should not be part of this observational registry and, if included, should be kept separate with a different consent from patients.

4) *Comparison of similar data elements*

When a field was present in two or in all three forms, a consensus was found to select the one that was thought to most accurately reflect the element explored and had the most accurate level of response.

5) *Sharing the new CRF with advocacy groups and industries representatives*

Once the items to be included in the new shared version were identified, the final list was shared with advocacy groups and patients in order to obtain feedback and suggestions on other fields that they thought could be relevant. Both felt that our list was exhaustive. Collaborating with epidemiologists from a biotechnology company engaged in drug development for SMA was particularly useful. The data elements and data dictionary discussions benefitted from having this different perspective and anticipating how the data might eventually be utilized.

6) *Simplifying the level of responses to increase accuracy*

Once the final list of items was achieved a consensus was found on the items to be included in the baseline visit or in the follow up form. The form was then discussed with an external CRO that converted our forms into an electronic case report form (eCRF) and provided some help on how to optimize the accuracy of the responses. Agreement was sought on the definition of each data element. The goal was to clearly define each data element with a list of specific choices and to avoid free text answers. Fields with open answers were converted as much as possible into multiple prespecified answers in order to reduce the possible variability of the responses and the difficulties in aggregating data. Similarly, company representatives suggested to use a more structured format to record concurrent diseases, using an internationally accepted format for other disease registries, using the Agency for Health Quality Research and Quality Clinical Classification Software (CCS) coding system.

7) *Data dictionary*

Considerable effort went into defining a common data dictionary to enable harmonized data collection. Each data element was discussed by participants of the 3 networks in order to make sure that clear definitions would be available for each field and that there were no cultural differences in the interpretation of the wording explaining each item.

3. Results

8) *Piloting the first version*

The first newly harmonized eCRF was piloted in all the centers of the network, involving participants who had not been involved in the development of the eCRF, in order to ascertain if the forms were easily understood and could easily be filled. A number of suggestions were made to amend fields where the examiners felt that instructions were not sufficiently clear or could be misinterpreted.

The final version of the forms includes hundreds of data fields collecting detailed information on clinical features, supportive care, functional measures, hospitalizations and other health related issues. Table 2 shows a conceptual overview. Biobanking of patient samples as well as patient-focused aspects such as patient reported outcomes and health-related quality of life are planned to be included in the data collection in the near future.

9) *Study population and data collection*

Because the registry effort is aimed at understanding patients in the ‘real world’ of clinical care, all patients with diagnosed 5qSMA and not currently enrolled in a clinical trial are eligible for inclusion into the registry following informed consent. There was no pre-specified sample size. Data collection using the eCRF commenced by September 2018 in all networks. Data are collected at regular clinical intervals, in accordance to the clinical routine schedule, and entered into a registry database. This is a disease registry that is agnostic to treatments that patients may elect to take. Both untreated and treated patients are to be enrolled. Effort is made at each site to capture as many patients as feasible and minimize selection bias. A 15-year life cycle is anticipated. A number of additional issues were discussed.

Physiotherapy training sessions are conducted on a annual basis to ensure quality control of the outcome measures studied.

Table 2
Data collected in the registry (not an exhaustive list).

Motor milestones and functional assessments	Patient characteristics
• WHO Motor Milestones • CHOP-INTEND • HFMSE • Revised Hammersmith Assessment • HINE Section 2 • RULM	• Genetic confirmation • SMA Type • SMN2 Copy number • Diagnosed by NBS • Age at onset • Growth status • Ventilation status • Swallowing problems • Treatment with nusinersen (including administration details) • Treatment with other SMA specific drug • Procedures including scoliosis rods • Hospitalizations & causes • Mobility devices • Physio & Occupational therapy • Labs including liver chemistry • Additional data fields

CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE: Hammersmith Functional Motor Scale Expanded for SMA; HINE: Hammersmith Infant Neurological Examination; RULM: Revised Upper Limb Module.

10) *Informed consent, privacy protection and ethical committee reviews*

Each patient included in the registry provided informed consent. Each participating iSMAc site gained approval for the study procedures from their local ethic committee/institutional review board. Privacy protection was identified early in this process to be a critical issue and that each network needed to abide by country-specific laws. This created a challenge as variability in these patient protection laws prevented simple combining of patient specific de-identified data. It became necessary for each network to collect appropriate patient data from the individual sites, in keeping with local ethic committee review, collating this data into a national registry, and then determining how much of this data can be exported into a central electronic data repository.

11) *Data ownership, intellectual property rights and data sharing agreements*

These aspects were first developed within each network and then among the networks and with any industry or advocacy group partners. In Italy and UK the data are owned by the individual centers collecting the data and the informed consent allows data sharing for academic and regulatory purposes. In Italy, because of a more restrictive privacy rules, only aggregate data can be provided.

In the US centers patients own their personal data and agree to share de-identified data according to terms outlined in the informed consent document signed by each participant.

Funding to support this effort was procured initially from Biogen. Other pharmaceutical companies involved in therapeutic development for SMA are also currently interested in supporting our academic effort. The goal is to have equitable and transparent funding form all interested parties with the involvement of third parties such as advocacy groups and ethicists that are currently engaged to create a committee supervising data availability and ethical aspects.

The initial year was spent in developing the initial usable version of the SMA registry and in piloting data collection and entry within each network. Within one year from the start of data collection approximately 800 patients have been enrolled into the iSMAC registry.

4. Discussion

The iSMAR was established in 2017 and links 3 national networks originally funded by their national advocacy groups. These 3 networks have a long standing tradition of academic collaboration, that contributed to the development of novel and SMA specific outcome measures used in natural history studies [8–10,15–29]. All three networks have been involved in long term observational studies, capturing natural history data using structured assessments and with a clinical trial approach. This included training of the evaluators and use of CRFs that have helped to collect some additional data (SMN2 copy number, etc.) that have helped the interpretation of the functional data and to stratify the patients. The registries of functional data from these three networks includes prospectively collected data from over 800 SMA patients ranging from infants with SMA I to adults with SMA III that have largely contributed, independently or, more recently, in collaboration, to define trajectories of progression in SMA patients. These early collaborative efforts prompted the need to update and upgrade the 3 registries with the creation of a common disease registry. Since 2017, iSMAc has been collaborating with Biogen to develop of a shared academic registry to capture the evolving history of SMA patients. The aim of our project was to develop a registry that while still maintaining the rigorous collection of functional data with structured data collection forms and regular training sessions of the evaluators to ensure quality control, would also include a number of additional data to define the disease burden and the impact on the health system in all types of SMA. The focus in the last years has been mainly on establishing the efficacy and the impact of nusinersen as it has become commercially available. Our effort is consistent with the EMA's guidance that registries include both drug-treated and untreated patients. Opting for a general disease registry has also the advantage that we will be able to continue our prospective longitudinal data collection in the untreated patients. Furthermore, with new treatments under discussion with regulators, a disease registry will also give the opportunity to collect patients on different or combinatorial treatments.

Initial efforts focused on identifying data elements. There was a very high concordance on the data included in the

original CRF from the three networks. After a selection of the existing fields, each network was asked to provide a list of possible additional items. There was a strong consensus that details of the supportive care, number and type of hospitalization, and in general any other medical intervention should be captured in more detail in order to have a more accurate estimate of the burden of the disease and of the impact on the health system. The list of old and new data elements was shared first with patients and family representatives in order to have their perspective, and to identify elements that may have been neglected but were still relevant in every day life for the patients and their carers. Similarly, the form was shared with Biogen representatives who also provided suggestions on a more structured way to record concurrent illnesses, using a system that is standardly used in registries.

After piloting the first version and amending it according to the feedback received, the final version of the registry has been shared with other networks and advocacy groups, with the hope that at least the data dictionary and some basic common data elements could be shared. The form was shared with other companies who had drugs for SMA in their pipeline or in current clinical trials, and they all had only minimal comments or suggestions, mainly related to the need to add patient/carer related outcome measures and to ensure capture of drug specific events.

The final version has now been systematically used for over a year, and currently more than 800 patients are registered, with more than half having already more than one follow up assessment at the time of writing. When developing this new combined CRF module, particular care was devoted to link the new data collected with data collected in the past by the three networks in natural history studies using the same functional measures. This allows us to provide longer term natural history data in untreated patients, and to compare the trajectories of progression before and after treatment in patients who started treatment or had any significant change in their care.

Due to the quality control of the data collected and the regular training of the investigators and therapists, such a registry can potentially be used for postmarketing purposes. The registry collaboration between Biogen and iSMAc is one of five studies recently included in an EMA publication on the use of real world evidence for regulatory purposes [30]. A challenge of collecting high quality data is that centers with sufficient resources to conduct research are often providing the highest standards of care, which in turn limits the generalizability of the data collected. Ongoing discussions with other registries under development will hopefully allow sharing of at least a minimal dataset and promote some degree of alignment of the data being collected.

iSMAC Group

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