Development of a Duchenne Muscular Dystrophy registry for children in South Africa to optimize care

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Background

Duchenne Muscular Dystrophy (DMD) is the most prevalent and lethal of the inherited dystrophies. Globally, the incidence is reported at 1 in 3500 live male births. There is currently no cure for the disease. With the possibility of gene therapy becoming available, patients who would qualify for such treatment need to be identified. Further, understanding disease expression in a population is essential to focus targeted interventions, such as corticosteroids, to ensure they are safe and effective in the local setting. By maintaining a DMD specific disease registry this information can be attained.

Objective: This report describes the concept and design of the first South African DMD disease registry using Research Electronic Data Capture (REDCap)

Methods: The registry was developed using REDCap’s web-based online design, accessed through the Clinical Research Centre (CRC) in the Faculty of Health Sciences at the University of Cape Town. Electronic case report forms were created from these clinical data using REDCap and for specific variables serial entries were possible relating to disease progression. International data standards were adopted as proposed by TREAT-NMD, a global network of registries on DMD to ensure our data is compatible with this and other international registries.

Results: Retrospective data entry combined with dynamic prospective recording of data was utilized in this project. Building on an existing database, 100 confirmed DMD boys are currently eligible for inclusion into the registry.

As our registry is an on-going study, sequential analysis of accumulated data will be done going forward to review trends on our patients with DMD.

Conclusions: This report describes the concept and design of a DMD registry and the steps followed to its establishment with REDCap. The focus is to consolidate clinical and genetic information on South African patients with DMD, commencing with the local centre’s patient cohort but rolling out access to other South African centres to create a national resource, which is internationally relevant. Ideally this template could be duplicated in the conceptualisation of disease registries for other key conditions.
Background

Duchenne muscular dystrophy (DMD) is the most prevalent and lethal of the inherited dystrophies. Globally, the incidence is reported at 1 in 3500 live male births [1, 2, 3, 4].

Mutation of the dystrophin gene results in DMD, Becker muscular dystrophy (BMD) and a third intermediate form of muscle disorder, collectively known as the dystrophinopathies [1]. Muscle fibre degeneration is the primary pathologic process, leading to weakness as the principal symptom.

The different types of mutations described to date for the DMD gene include large deletions, duplications, point mutations and small rearrangements [2,5].

Internationally accepted guidelines support corticosteroid use, cardiac interventions and non-invasive ventilation, which are associated with better health outcomes, duration of survival and improved quality of life, but have no effect on modifying ongoing disease progression [6, 7, 8]. Postulated treatment strategies are geared towards alleviating the defective gene mutation [9,10]. Identifying the type of mutation that is linked to specific DMD phenotypes is central to genetic diagnosis – and to meaningful research – to ensure standardisation of clinical care. Over 7000 (7149 as of November 2013) mutations are listed in the global database, TREAT-NMD [2]. Even though establishment of these databases has led to increased awareness around disease registries and serves as an essential tool for improving quality patient outcomes, the number of established national disease registries are few [11, 12, 13]. Individual countries lack sufficient numbers of affected patients to embark on translational research [14]. Major barriers to recruitment into clinical trials are the lack of harmonisation and the prevailing fragmentation in the neuromuscular community with diverse geographic spread of patients [15].

Rare diseases, such as DMD, are reported to have a low prevalence; however, when considered together, they equate to large numbers, approaching millions in the USA, the European Union (EU) and Australia [3,14]. There is a paucity of rare disease data in Africa because of limited resources. Only two national registries exist for DMD: one in Sudan and one in Algeria. These registries are both linked to the TREAT-NMD database in Europe [3].

There is an evolving urgency for the formation of rare disease registries worldwide. This is especially the case in Africa, where collation of disease data is often limited and challenging [16].

The formation of rare disease registries is typically motivated by advocacy groups [17]. Rare Diseases South Africa, a voluntary organisation providing advocacy, awareness and support for people affected by rare diseases, and the Muscular Dystrophy Foundation of South Africa, a registered non-profit organisation whose mission statement is ‘to support people affected by Muscular Dystrophy and Neuromuscular disorders and endeavour to improve the quality of life of their members’, are examples of such advocacy groups in South Africa. Internationally, a Network of Excellence, funded by the EU, was launched on 1 January 2007. This network was named TREAT-NMD and has enabled experts to create common standards of care and bring together the neuromuscular community to escalate clinical trials and increase awareness of rare diseases such as DMD [3].
In South Africa, the dedicated neuromuscular service at the Red Cross War Memorial Children’s Hospital (RCWMCH), a university-affiliated teaching hospital in Cape Town, manages the largest group of children with DMD in the country.

The neuromuscular service follows international guidelines with a multidisciplinary team approach and input from ancillary services, including pulmonology, cardiology, child development, orthopaedics, histopathology, medical genetics and genetic counsellors. With the possibility of treatment becoming available, children who would qualify for targeted treatment need to be identified. The service has established a database of these children with confirmed DMD. Many of these children have been managed for over a decade and there are multiple variables of disease course for each individual child. This information needs to be consolidated into a patient registry to permit longitudinal comparisons of individuals as well as groups of children for common areas such as cardiac function in response to corticosteroids.

The South African DMD (SADMD) registry is the first resource which will consolidate clinical and genetic information on South African DMD patients with the potential to be considered for contemporary clinical trials as well as inform practice regarding the most recent and up-to-date standards of care. This cohort will provide the largest longitudinal data collection of children with DMD in Africa with the possibility to link with TREAT-NMD.

**Aim**

This study describes the concept and design of the first DMD disease registry in South Africa using Research Electronic Data Capture (REDCap).

**Objectives**

The objectives for forming the registry are:

- To update and expand the existing database and to populate it with current information relating to the clinical phenotypes of the affected children inclusive of their cardiac, respiratory, cognitive, oromotor/gastroenterological, motor and orthopaedic evolution.

- To assess the effect of the introduction of corticosteroid and cardiac interventions on the course of these children for their cardiac and pulmonary function, duration of ambulation, orthopaedic complications and resultant need for bilevel positive airway pressure (BIPAP) support.

- To correlate the clinical profiles of this patient group with those who have confirmed genetic mutations and identify those patients who may be suitable for the latest gene therapy and who would benefit from extended screening to confirm this is the case.

- To establish if the South African cohort carries a similar range of mutations to those listed internationally.

- To determine whether genotype–phenotype correlations exist.

- To identify if the range of patients carrying potentially remedial gene therapy mutations is in line with the incidence reported internationally.

**Methods**

**REDCap application**

Following the key recommendations of TREAT-NMD on creating registries for rare diseases
The SADMD registry is being developed as a robust software solution. The REDCap framework was chosen as it is a secure, Web-based application designed to support data capture for research studies, providing an intuitive interface for validated data entry; audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to common statistical packages; and procedures for importing data from external sources. The REDCap tool is hosted and managed by the University of Cape Town’s (UCT) eResearch Centre and the UCT Clinical Research Centre (CRC).

Vanderbilt University, Nashville, TN, developed the REDCap application, but it is available free of charge to institutional partners who satisfy the basic criteria for a Web server that supports secure socket layers/hypertext processor, MySQL database connections [18,19]. UCT satisfied all these criteria and has become a REDCap consortium member.

**DMD patients**

All children with a confirmed diagnosis of DMD according to DNA confirmation, compatible confirmation on muscle biopsy or with a confirmed affected relative where there is compatible X-linked inheritance are eligible for inclusion. Currently, only children managed through the RCWMCH neuromuscular service will be included, as these patients receive standardised and consistent care protocols which are not routine at this stage in other South African centres with less capacity. The service has international accreditation as a DMD-certified care centre based on the Parent Project screening process. The known genetic mutations of these children will be correlated to their clinical profile and their potential to undergo further screening for gene therapy.

Exclusion criteria for this database are children referred with a presumed diagnosis of DMD/BMD who subsequently were found to have other pathologies. Similarly, children suspected to have DMD/BMD but who lacked the definitive diagnostic closure via DNA analysis or muscle biopsy or family history were also excluded. In isolated cases children with known DMD were excluded when there was insufficient information documented or they were lost to follow-up.

The protocol for this study, the patient information and authorisation and relevant supporting information were all submitted, reviewed and approved by the Hospital Research Committee and the UCT Human Research Ethics Committee (HREC 001/2016).

For every affected child and carer, appropriate patient/caregiver assent/consent is obtained according to South African regulations. As the study is non-invasive and collating existing data, telephonic consent can be taken initially and formally signed at the caregiver’s convenience when they attend the clinic.

**Registry description**

In collaboration with the CRC in the Faculty of Health Sciences at UCT, the lead author developed the database using REDCap’s Web-based online designer. This database is shown in Figure 1. The online designer on REDCap will allow project modifications to fields and data collection instruments very easily using only the Web browser.

The enrolment and background data forms are developed to capture the mandatory set of data including age at presentation, first symptoms at presentation, demographics, family history, referral route and initial creatinine kinase values. This mandatory section is crucial for a meaningful data collection going forward so that each patient has a minimum amount of information recorded. The rest of the items focus on DMD-defined clinical manifestations and such data are collected in other sections of the registry listed above, repeated annually and as appropriate. Self-reported activities of daily living (ADLs) capture a patient’s reported quality of life on an annual basis to encourage active participation.
Figure 1. Figure 1 Screen shot of data forms as shown on REDCap.

The registry operates on a longitudinal module and utilises the repeating events feature of REDCap, which allows one to repeat an entire event of instruments together in unison. This is useful for several instruments whose data correlate. The repeating events feature allows one to create only one single event that can be repeated in an unlimited fashion.

Hospital clinical records and clinic visits are our main source of data, prospectively and retrospectively to be uploaded on an annual basis starting from the first documented visit to the neuromuscular service of RCWMCH, which then continues as dynamic longitudinal data collection. Children are clinically reviewed every 3–6 months.

Statisticians and information technology specialists reviewed the database design and planning process and provided detailed advice on the methodology and data items.

Creating the registry database

The REDCap server provides training videos and teaching resources on REDCap to guide users, such that formal training or prior experience is not required to use the application.

The CRC overseeing REDCap at UCT was consulted to assist with project programming, and to guide on data quality and security as well as to agree with the standard operating procedures. The implementation included defining variables and their properties, dataset preview and testing in anticipation for statistical output and analyses, and rights and permissions to users.

Data entry and quality

Data entry errors are a possibility and test runs are important to try to curtail errors as much as possible. The REDCap data quality module allows for execution of data quality rules upon project data to check for discrepancies in data; this feature was utilised in this project and predefined rules filtered errors and discrepancies. These predefined rules were important since our registry consists of many fields and records. Data validation was possible as a REDCap feature by limiting datasets and set ranges for numerical data fields; the data quality module reports any values out of range, incorrect data type and outliers.

The main investigator pioneered the data extraction and input, with review, adjustments and additions by the supervisor.

Database management

This project is primarily managed by the neuromuscular service of the RCWMCH.

Results

Retrospective data entry combined with dynamic prospective recording of data was utilised in this project. Building and expanding on an existing Excel database, 100 boys with confirmed DMD are currently eligible for inclusion into the registry.

Structure of the registry

The registry database consists of seven forms collecting information on enrolment, background details, current disease, schooling/career prospects, ADLs, power chart and current motor
function/symptoms; these are subdivided into 100 items, making a total of 210 variables, as shown in Table 1.

<table>
<thead>
<tr>
<th>Enrolment details</th>
<th>Study ID, consent/assent done, date subject signed consent, currently included in a clinical trial/study, trial/study name, name of person doing the entry, name, date of birth, age, gender, address, next of kin, ethnicity, race, primary condition, diagnosis code, presumed clinical subtype, date diagnosed, age at diagnosis, muscle biopsy details, genetic details, gene therapy eligibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background information</td>
<td>Age at first symptoms, type of symptoms presented with, hospital admissions and reason for admission, best motor function, wheel chair use, age of starting wheel chair use, type of wheel chair, source of wheel chair, age of complete loss of ambulation, family history of DMD, CPK test details, referral details of patient</td>
</tr>
<tr>
<td>Current disease on annual basis</td>
<td>Weight, height, BMI, respiratory involvement and respiratory co-morbidity, NIV, form of NIV, indication for NIV, type of NIV, form taken, tracheostomy details, special investigations, lung function details, chest infection episodes, result of polysomnography, need for pulmonology referral and reasons for doing so, chest physiotherapy details, steroid use, date steroid started and reason for starting, current steroid dose and regimen, side effects so far, scoliosis and cardiac involvement, bone health, physical therapy interventions, nutritional management</td>
</tr>
<tr>
<td>Schooling/career prospects</td>
<td>School curriculum; lifestyle and psychosocial issues such as education on DMD, emotional issues, social support and support grant; type of support grant</td>
</tr>
<tr>
<td>Basic activities of daily living</td>
<td>Bathing, dressing, toileting, transferring, continence, feeding, MRC average score (×5), Gower’s time score, 6 minute walk test</td>
</tr>
<tr>
<td>Power chart</td>
<td>Able to walk, able to run, able to climb stairs, arm involvement, participates in sports, myalgia, time myalgia is experienced</td>
</tr>
</tbody>
</table>

Table 1. Table 1. DMD registry structure

Clinical data standards

This registry has been set up to consolidate known clinical data in preparation for translational research. In this regard, the dataset for collection is concise and guided by pertinent aspects of required inclusion criteria for clinical research, known as the mandatory dataset. The variables and items described above are all based on standardised elements proposed by TREAT-NMD data standards [3]; the defined dataset allows a coordinated approach to clinical trial readiness and our records to be comparable and anonymously aggregated.

In addition to the mandatory dataset, additional data will be collected that are unique to our population group, such as items relating to ADLs of our patients and the natural history of the disease, to look at other variables of interest to the neuromuscular service here at RCWMCH.

Data storage

Figure 2 shows a screen shot of part of the current responses and records with their status for every event and data collection instrument. Clicking on a button opens a new tab/window in the browser to view the record on that data collection instrument. We provide form-level user privileges to restrict certain data collection instruments, so that users can only view those instruments that are related to their user rights data access group.
This also shows the enrolment visit (visit 0), and annual visits. On enrolment, all instruments are administered or completed for baseline minimum data on all children. On annual visits, the enrolment form and background data are not repeated, but the remainder of the instruments are repeated to enable us to determine any trends. This task is possible by utilising the repeat instrument functionality of REDCap.

**Figure 2.** Screen shot of part of the DMD registry, status dashboard.

**Security of data**

Users are granted access to this project and user privileges of those users are managed by the project administrator; this provides complete patient confidentiality since all information is encrypted in the REDCap server. Roles can be created to which users are assigned. User roles are useful when there are several users with the same privileges. Roles and rights can be given for access across many tasks ranging from managing participants, file repository, logging, data export, data import, data entry rights, project design and calendar to data quality. Logging is required for every encounter with the data, providing an audit trail. The registry administrator has, in addition, the privilege to lock the data after all finalisation checks. UCT unique user names and passwords are required for researchers to access the database (**Figure 3**).

This means that the SADMD registry is an authentication-based system and, when rolled out nationally, will be broadly broken into two sections: the component available to authenticated users and that available to unauthenticated users.

Only one page of the DMD registry will be available to unauthenticated users: a landing page explaining the aims of the registry, as depicted in **Figure 4**.

**Figure 3.** Granting user rights and permissions.

**Figure 4.** Potential landing page for unauthenticated users of DMD registry.

**REDCap advantages in data collection to support research**

The project brought forward a host of advantages to using the REDCap application for registry design and identified very few challenges in the design of the electronic case report forms.

The ease of form construction was noted to be a major advantage. Forms were created by a point-and-click interface on the Web; data dictionaries externally created in Excel can be uploaded. Moreover, UCT’s eResearch Centre and the UCT CRC technical team allowed quick answers to questions regarding technical difficulties in the design, particularly on the use of piping and branching logic and so on.

Equally important when using the REDCap application was the clear and easy way of creating customised reports and exporting the data. Multiple data formats can be exported for use in various statistical software.

Rapid quality assessment, associated with the software, made it possible to identify data errors, which were corrected by the neuromuscular team on a continuing basis. Data elements and entry forms are specific; this was an advantage in avoiding errors on entering records.
However, challenges and limitations were identified in the creation of this registry using the REDCap application. This was illustrated via a piloting stage when entry form problems were noted. This warranted the REDCap main administrator to archive the old entry forms, temporarily take down the database, fix the errors and restart the database. Therefore, meticulously reviewing the data instruments prior to ‘going live’ and testing and retesting them rigorously and imaginatively are encouraged.

Nonetheless, these limitations and challenges are not major when compared with the advantages stipulated above. This registry demonstrates that REDCap is indeed an effective tool in collecting research and clinical data.

**Discussion**

This DMD registry is built on the need to consolidate clinical and genetic information on South African DMD patients. Clinical and translational research is needed and should be based on the most recent and up-to-date standards of care. In this report, we describe the concept and design of our DMD registry. We adopted a range of steps, including: meticulous database planning, the use of REDCap to construct the electronic case report forms as well as adopting clinical data standards.

This study method is also an attempt to follow international efforts in data consolidation through a reproducible research protocol, making it possible for replication to other medical registries. To conform to this, we adopted international data standards proposed by TREAT-NMD, a global network of registries on DMD, funded by the EU. This allows for internationalisation of our registry; accordingly, we followed the defined standard items recommended by TREAT-NMD [3,16] as well as data elements from other international designs such as the NorthStar Clinical Network for paediatric neuromuscular disease (NSCN) established in the UK at the end of 2003, with the objective of optimising the care of and acquiring longitudinal natural history data on boys with DMD; the NSCN has 17 participating specialist paediatric neuromuscular centres. A secure Web-based database has been used for data collection since 2006 [20].

Electronic information in health systems is now recognised and accepted in the international community, making it crucial to adopt established data standards. Consequently, this means a more versatile registry and the possibility of our registry being able to collaborate with other institutions as well as linking with TREAT-NMD.

Successful workflow models aligned to daily and clinical practice with minimal interruption has produced successful registries [12,16,21, 22, 23]. In our work, we have aligned the clinical services of the neuromuscular unit to consenting and asking patients and caregivers to allow for their information to be uploaded.

Our data collection primarily focuses on background information, diagnosis, interventions and genetic data, which are all essential to identifying subjects eligible for clinical and translational research.

As our registry is an ongoing study, sequential analysis of accumulated data will be done going forward to review trends on our patients with DMD. As a result we will aim to provide evidence-based decisions for patients with DMD in our setting. The registry data will be used to assess the effect of the introduction of corticosteroids and cardiac interventions on the course of these children for their cardiac and pulmonary function, duration of ambulation, orthopaedic complications and the resultant need for BIPAP support. Also, to correlate the clinical profiles of this patient group with those of patients who have confirmed genetic mutations, and to identify who may be suitable for the latest gene therapy and who would benefit from extended screening to confirm if this is the case. The registry will establish if the South African cohort carries a similar range of mutations to those listed internationally. Further the data will establish if
genotype–phenotype correlations can be identified between specific mutations and the clinical course, as well as the prevalence of patients carrying potentially remedial gene therapy mutations compared with that reported internationally.

Conclusions

This work describes the concept and design of a DMD registry and the detailed steps followed for its establishment with REDCap. The focus is to consolidate clinical and genetic information on South African patients with DMD that will translate to clinical research and to form the basis for these children’s information to be linked internationally. Ideally this template can be re-used in the conceptualisation of new disease registries.

List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADL</td>
<td>activity of daily living</td>
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<tr>
<td>BMD</td>
<td>Becker's muscular dystrophy</td>
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<tr>
<td>DMD</td>
<td>Duchenne muscular dystrophy</td>
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<tr>
<td>BIPAP</td>
<td>bilevel positive airway pressure</td>
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<td>BMI</td>
<td>body mass index</td>
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<td>CRC</td>
<td>Clinical Research Centre</td>
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<td>CPK</td>
<td>creatinine phosphokinase</td>
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<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>ID</td>
<td>identification</td>
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<tr>
<td>NIV</td>
<td>non-invasive ventilation</td>
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<tr>
<td>NMD</td>
<td>neuromuscular disease</td>
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<tr>
<td>REDCap</td>
<td>Research Electronic Data Capture</td>
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<td>RCWMCH</td>
<td>Red Cross War Memorial Children's Hospital</td>
</tr>
<tr>
<td>SADMD</td>
<td>South African Duchenne muscular dystrophy</td>
</tr>
<tr>
<td>TREAT-NMD</td>
<td>neuromuscular registry in Europe</td>
</tr>
<tr>
<td>UCT</td>
<td>University of Cape Town</td>
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</tbody>
</table>

Table. List of abbreviations

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Conflict of Interest Disclosure:

All authors declare no conflicts of interest.

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Authors’ contributions:

J.M.W. and A.A.J. conceived the presented idea. A.A.J. developed the Registry. A.N., W.M. and
T.-M.W. verified the design and methods. J.M.W. encouraged A.A.J. and supervised the findings in this work. All authors discussed the results and contributed to the final manuscript. J.M.W. proof read and contributed to the report content.

Disclaimer:

Opinions expressed in this manuscript and the conclusions arrived at are those of the authors, and are not necessarily to be attributed to the UCT Master’s Fund Committee.

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