Academic Productivity from Rare Neuromuscular Disease Registries: A Systematic Review

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Neuromuscular Registry
TREAT-NMD
TGDOC
Rare disease
Real-World evidence

ABSTRACT

Background: TREAT-NMD is a global neuromuscular (NM) organization, created to enhance infrastructure to facilitate novel therapeutics reaching patients. One main activity is aimed at supporting NM disease registries. These rare disease registries are useful to fill knowledge gaps for various stakeholders in the disease community using real world data. Although it is important to understand how patient data is being utilized in the TREAT-NMD network and other rare disease registries, there is no systematic process or consistent metric for documenting the academic output from these registries.

Objectives: The objective of this study was to determine the academic output from NM registries associated with the TREAT-NMD network, and the types of research the data is facilitating.

Results: A systematic search of EMBASE, Medline, Cochrane Central and SCOPUS was performed from inception to November 24, 2021. The search yielded a total of 650 results, with 231 full text studies assessed for eligibility and a total of 97 studies that met the inclusion criteria.

Conclusions: The results suggest publications from TREAT-NMD are mainly descriptive or methodologic. Rare disease registries, like the TREAT-NMD network, would benefit from clear and consistent metrics to facilitate reporting of academic output.

Introduction

TREAT-NMD is a neuromuscular network established in 2007 that provides infrastructure to help the development and translation of novel therapies to patients and establish best practice guidelines for neuromuscular disease (NMD) patients worldwide. The network was started as a European Union Network of Excellence, but has since developed into a self-sustaining international organization, uniting patients, clinicians, researchers, and industry in efforts to accelerate therapies for NMD (treat-nmd.org). The organization has several pillars of work with one of the primary efforts to support rare NMD registries. Patient registries have become an important research infrastructure tool for NMD facilitating epidemiologic studies, natural history profiles, clinical trials, and post marketing surveillance. Not only do these patient registries allow eligible patients to be connected to clinical trials, they also allow research
and questionnaires on care and disease progression to be efficiently conducted. This is especially important for rare neuromuscular conditions where small patient populations jeopardize clinical trial enrollment. Patient registries serve to mitigate this risk through proper trial planning and recruitment. TREAT-NMD has established an oversight group (TREAT-NMD Global Data-systems Oversight Committee, TGDOC) to support NMN registry development and implementation, sustain relationships, and encourage best practices for NMN registries across the globe. Currently there are over 40 national and international NMN registries focusing on over 10 unique NMNs from over 25 countries affiliated with TGDOC (please see: https://treat-nmd.org/patient-registries/list-of-registries-by-disease for information on each registry). The various NMNs registries include: Charcot marie tooth disease, congenital muscular dystrophies, congenital myasthenic syndromes, Duchenne/Becker muscular dystrophy, Facioscapulohumeral muscular dystrophy, GNE myopathy, Limb girdle muscular dystrophies, MTM and CNM registries, Myotonic dystrophy, and spinal muscular atrophy.

One of the primary objectives of NMN and other rare disease registries are to use the real-world data to fill knowledge gaps for various stakeholders in the disease community. This includes facilitating research and studying the patient populations of interest, with the overall goal of improving patient outcomes. However, there remains sparse literature regarding how to best measure the academic output, such as peer reviewed publications or scientific meeting presentations, from registries and the factors that contribute to productivity. These registries contain vast amounts of patient data and ought to be a source of significant academic activity.

Presently in the TREAT-NMD registry network there is no systematic process of documenting the academic output from the registries, however this is important to understand how patient data is being used in the constituent registries. The purpose of this study is to determine the amount and type academic output from TREAT-NMD registries, and the types of research the data is facilitating.

Materials and Methods

This systematic review followed the PRISMA 2009 guidelines. A systematic search of EMBASE, Medline, Cochrane Central and SCOPUS was performed from inception to November 24, 2021. An additional search of SCOPUS was also performed on November 24, 2021 to identify any relevant studies that mentioned TREAT-NMD in the funding and acknowledgements section. The search strategies are listed in Supplementary Appendix.

Study selection and eligibility criteria

Studies were eligible for inclusion based on two criteria: 1) The primary content of the study was related to a neuromuscular disease and 2) The study finding, or results were generated using data directly from a TREAT-NMD registry. The study must specifically mention that the data was obtained from a TREAT-NMD registry. All study types whether in abstract or published manuscript form were considered for inclusion.

Two authors (CC and RS) independently screened the titles and abstracts, and selected articles for full text review. Full text articles were then reviewed for eligibility, with arbitration by a third author (TMN) for any differences that could not be resolved by consensus. We identified and removed duplicates if the studies appeared in multiple databases and if the same study was presented at multiple academic forums/meetings.

Eligible studies were then sub-grouped into four different categories including: Profile or methodologic, clinical research/guidelines, epidemiologic and basic science. Eligible studies were characterized as either abstracts or published manuscripts.

Results

The search yielded a total of 650 results, with 231 full text studies assessed for eligibility and a total of 97 studies included in the final analysis (Figure 1). The main reason for excluding studies was because they did not include or use TREAT-NMD data in their study.

One of the studies was a basic science publication (manuscript), 22 were clinical research/guidelines (seven abstracts and 15 manuscripts) publications, six were epidemiology publications (four abstracts and two manuscripts) and 68 were profile/methodologic publications (31 abstracts and 37 manuscripts). In total, 42 were in abstract form and 55 were published manuscripts (Online Supplement).

It is worthy to note that publications may have been missed if they did not mention TREAT-NMD or TGDOC in the searchable fields, such as the title, abstract, keywords, and acknowledgements.

Discussion

The goal of this systematic review was to assess the type of academic output from the TREAT-NMD Global Database Oversight Committee (TGDOC). The TGDOC is a large network of largely academic and patient organization registries, containing data on thousands of patients. As part of fostering this network, it is important to showcase work from the constituent registries, as well as understanding the different type of academic output from this valuable real-world data. However, it became clear there was limited benchmarking in the literature to fully assess the typical levels of academic productivity from...
rare disease patient registries. Although rare registries may have different purposes and goals which may not include producing publications, the reality is that there is a substantial amount of patient data in these repositories. However, the results from this review appear to show that there is a relatively small amount of research addressing epidemiologic or clinical questions that comes directly from these patient repositories. Furthermore, the literature contains little methodological research examining how a registry governance, objectives, and structure link to academic productivity. Therefore, we hope this study contributes to the discussion regarding the need to have consistent metrics and an elevated level of responsibility to report academic productivity that can be anticipated from a rare disease registry.

From this study we can take that many registries do an initial publication highlighting their existence and describing the characteristics and implementation of the registry. This was seen in our sample with 70% of the published/presented academic work was a methodologic description of the registry. There are a smaller number of studies that use the data for addressing a particular scientific question. The clinical studies were largely survey type studies examining patient reported outcomes such as quality of life, burden of illness or adherence to standards of care. Aside from answering relevant scientific questions, publishing from a registry serves many useful purposes including: 1) increasing the awareness of the existence of registry; 2) demonstrating a responsiveness to the patients and NMD disease community; 3) publicizing how the registry is stewarding the data; 4) exposing the registries to constructive criticism on which to drive improvements; 5) contributing to interoperability and collaboration; 6) inviting inquiry for regulatory, medicine authorization and health technology assessment processes; and lastly, 7) strengthening the science around registry methodology.
to include their affiliation with TREAT-NMD in their future publications. Additionally, it is also possible that only the larger NMD centers/registries managed to publish relevant studies from their registries due to larger number of patients included. Smaller registries may need to merge under a TREAT-NMD/TGDOC, in a centralized registry to have the data used in a beneficial way for publication.

TREAT-NMD is a large inclusive organization that aims to advance diagnosis, care and treatment, facilitating the development of novel and existing therapies for patients living with NMD. We believe registries are an integral part of that effort but recognize there are still substantial steps in registry science and utilization efforts that need to occur to inform how registries can be better used as tools to facilitate research. There seems to be a need to develop pathways to better communicate and share registry data with all stakeholders, but more importantly with the patient stakeholders that have offered their valuable data to be included in registries.

Based on this systematic review, we plan to perform an additional similar review to search all rare NMD registries. This will hopefully allow us to achieve the objective of identifying all TREAT-NMD affiliated studies, as well as understand the patterns of academic productivity from registries. With a bigger sample size, we can also begin to try to understand other factors contributing to academic productivity. Factors such as size, location, affiliation with an academic institution, and the prevalence of the disease may influence the publication patterns.

**Competing Interest**

**TMN** has no conflicts of interest to declare.

**MD** has no conflicts of interest to declare.

**NB** is an employee of TREAT-NMD.

**VM** has no conflicts of interest to declare.

**HN** has no conflicts of interest to declare.

**DO** has no conflicts of interest to declare.

**SW** has no conflicts of interest to declare.

**NG** has been clinical trial site investigator for GSK, Biogen, Eli Lily, Pfizer, Roche, Sarepta, Wave and has served on advisory boards and/or Data Monitoring Committee for Sarepta, Wave, Biomarin, Pfizer, Avidity, Daiichy Sankyo, Avexis, Biogen.

**AA** has no conflicts of interest to declare.

**CC** has been a clinical trial site investigator for Acceleron, AMO, Biogen, Eli Lily, GSK, Biogen, Pfizer, Roche, PTC, Sarepta, Cytokinetics, Wave. Advisory functions: AMO, Biogen, Acceleron, Biogen, Roche, PTC. DSMB member: Catabasis and Solid.

**RES** has no conflicts of interest to declare.

**References**


Supplementary Appendix- Search Strategies

**SCOPUS**
1. Treat-NMD
2. Treat-NMD neuromuscular network
3. Treat neuromuscular disease
4. Treat-neuromuscular disease
5. Treat NMD
6. TREATNMD
7. TGDOC

**MEDLINE**
1. Treat-NMD*.mp.
2. Treat-NMD neuromuscular network.mp.
3. Treat-neuromuscular disease.mp.
4. Treat NMD.mp.
5. TREATNMD.mp
6. TGDOC.mp.
7. Or/1-6
8. (Becker muscular dystrophy or BMD).mp.
9. (Congenital muscular dystrophy or CMD).mp.
10. (Congenital myasthenic syndrome or CMS).mp.
11. (Charcot marie tooth or CMT).mp.
12. (Myotonic dystrophy or DM1 and DM2).mp.
13. (Duchenne muscular dystrophy or DMD).mp.
14. (Facioscapulohumeral muscular dystrophy or FSHD).mp.
15. (GNE myopathy or GNE HIBM).mp.
16. (Limb girdle muscular dystrophy or LGMD).mp.
17. (Congenital myopathy or Myotubular myopathy or Centronuclear myopathy or CFTD, MTM or CNM or MTM-CN).mp.
18. (Spinal muscular atrophy or SMA).mp.
19. (Neuromuscular* or neuromuscular disorder* or neuromuscular disease*).mp.
20. Or/8-19
21. 7 and 20

**EMBASE**
1. Treat-NMD*.mp.
2. Treat-NMD neuromuscular network.mp.
3. Treat-neuromuscular disease.mp.
4. Treat NMD.mp.
5. TREATNMD.mp
6. TGDOC.mp.
7. Or/1-6
8. (Becker muscular dystrophy or BMD).mp.
9. (Congenital muscular dystrophy or CMD).mp.
10. (Congenital myasthenic syndrome or CMS).mp.
11. (Charcot marie tooth or CMT).mp.
12. (Myotonic dystrophy or DM1 and DM2).mp.
13. (Duchenne muscular dystrophy or DMD).mp.
14. (Facioscapulohumeral muscular dystrophy or FSHD).mp.
15. (GNE myopathy or GNE HIBM).mp.
16. (Limb girdle muscular dystrophy or LGMD).mp.
17. (Congenital myopathy or Myotubular myopathy or Centronuclear myopathy or CFTD, MTM or CNM or MTM-CN).mp.
18. (Spinal muscular atrophy or SMA).mp.
19. (Neuromuscular* or neuromuscular disorder* or neuromuscular disease*).mp.
20. Or/8-19
21. 7 and 20

Cochrane CENTRAL
#1 Treat-NMD*
#2 Treat-NMD neuromuscular network
#3 Treat-neuromuscular disease
#4 Treat NMD
#5 TreatNMD
#6 TGDOC
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 Becker muscular dystrophy or BMD
#9 Congenital muscular dystrophy or CMD
#10 Congenital myasthenic syndrome or CMS
#11 Charcot marie tooth or CMT
#12 Myotonic dystrophy or DM1 and DM2
#13 Duchenne muscular dystrophy or DMD
#14 Facioscapulohumeral muscular dystrophy or FSHD
#15 GNE myopathy or GNE HIBM
#16 Limb girdle muscular dystrophy or LGMD
#17 Congenital myopathy or Myotubular myopathy or Centronuclear myopathy or CFTD, MTM or CNM or MTM-CN
#18 Spinal muscular atrophy or SMA
#19 Neuromuscular* or neuromuscular disorder* or neuromuscular disease*
#20 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#21 #7 and #20
### Table 1: Included Studies (N = 97)

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<th>Study</th>
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<td>Bushby K. Advancing diagnosis, care and treatment for people with neuromuscular diseases around the world: A network of excellence to catalyse research infrastructure globally. Orphanet J Rare. 2010;5.</td>
<td>Abstract Profile/Methodologic</td>
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<td>45</td>
<td>Bladen CL, Salgado D, Monges S, et al. The TREAT-NMD DMD global database: Analysis of more than 7,000 duchenne muscular dystrophy mutations. Hum Mutat. 2015;36(4):395-402. Published manuscript Profile/Methodologic</td>
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<td>47</td>
<td>Godoy AJ. The creation of a network after an international conference. Neuromuscul Disord. 2013;21 (9-10):722-723. Published manuscript Profile/Methodologic</td>
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<td>49</td>
<td>Kimura E, Nakamura H, Mitsuhashi S, et al. The infrastructure for the clinical research of muscular dystrophies: Remudy and MDCTN. Clin Neurol. 2014;54(12):1069-1070. Published manuscript Profile/Methodologic</td>
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<td>52</td>
<td>Lochmuller H. The TREAT-NMD patient registries for spinal muscular atrophy and Duchenne muscular dystrophy. Dev Med Child Neurol. 2009; 3:6-7. Published manuscript Profile/Methodologic</td>
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<td>57</td>
<td>Peay HL, Rangel VM, Brown K, Martin AS, Furlong P. New horizons in the Duchenne Connect registry. Neuromuscul Disord. 2011;21 (9-10):722. Published manuscript Profile/Methodologic</td>
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<td>58</td>
<td>Rautenstrauss B, Sereda MW, Walter MC. The prospective German Charcot-Mary-Tooth patient registry. Medizinische Genetik. 2010;22 (1):177. Published manuscript Profile/Methodologic</td>
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<td>60</td>
<td>Rodger S, Lochmuller H, Tassoni A, et al. The TREAT-NMD care and trial site registry: An online registry to facilitate clinical research for neuromuscular diseases. Orphanet J Rare Dis. 2013; 8:171. Published manuscript Profile/Methodologic</td>
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<td>84</td>
<td>Bayat F, Sarmiento IG, Ahmadian N, Dehghani Z. &quot;Iranian Registry of Duchenne and Becker Muscular Dystrophies: Characterization and Preliminary Data.&quot;</td>
<td>Published manuscript Profile/Methodologic</td>
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<td>88</td>
<td>Imber, L. and V. Straub. &quot;Registries and care of NMD: The international GNE myopathy patient registry.&quot;</td>
<td>Abstract Profile/Methodologic</td>
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<td>90</td>
<td>Lusakowska A, Jedrzejowska M, Kaminaska A, et al. &quot;Observation of the natural course of type 3 spinal muscular atrophy: data from the polish registry of spinal muscular atrophy.&quot;</td>
<td>Abstract Epidemiology</td>
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<td>93</td>
<td>Porter B, Turner C, Monckton D, et al. &quot;Myotonic Dystrophy: Characterising myotonic dystrophy (DM) and supporting national and international research projects: nine years of the UK DM patient registry.&quot;</td>
<td>Abstract Profile/Methodologic</td>
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<td>94</td>
<td>Raynaud S, Viscidi E, Hall S, et al. Utilization of real-world observational data to study safety and effectiveness of spinal muscular atrophy treatments.</td>
<td>Abstract Profile/Methodologic</td>
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<td>96</td>
<td>Sherif RE, Gamal M, Hanafy A. &quot;Registries and care of NMD: The Egyptian neuromuscular registry.&quot;</td>
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