NARCOMS and Other Registries in Multiple Sclerosis

Issues and Insights

Ruth Ann Marrie, MD, PhD; Gary R. Cutter, PhD; Robert J. Fox, MD, MSc; Timothy Vollmer, MD; Tuula Tyry, PhD; Amber Salter, PhD

CE Information

Activity Available Online: To access the article, post-test, and evaluation online, go to https://www.highmarksce.com/mscare.

Target Audience: The target audience for this activity is physicians, physician assistants, nursing professionals, and other health care providers involved in the management of patients with multiple sclerosis (MS).

Learning Objectives:

1) Describe what constitutes a registry.
2) Discuss the difference(s) between clinician-driven and patient-driven registries, including potential advantages of patient-driven registries.

Accreditation Statement:

In support of improving patient care, this activity has been planned and implemented by the Consortium of Multiple Sclerosis Centers (CMSC) and Delaware Media Group. The CMSC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physician Credit: The CMSC designates this journal-based activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurse Credit: The CMSC designates this enduring material for 1.0 contact hour of nursing continuing professional development (NCPD) (none in the area of pharmacology).

Disclosures: **Francois Bethoux, MD,** Editor in Chief of the *International Journal of MS Care* (IJMSC), has served as Physician Planner for this activity. He has disclosed relationships with Springer Publishing (royalty); Qr8 (receipt of intellectual property rights/patent holder); Biogen (receipt of intellectual property rights/patent holder, speakers' bureau); MedRhythms (consulting fee, contracted research); GW Pharmaceuticals, Genentech, Helius Medical Technologies, Osmotica, Ipsen (consulting fee); and Adamas Pharmaceuticals (contracted research). **Ruth Ann Marrie, MD, PhD,** has disclosed being a co-investigator on a study funded by Biogen and Roche. **Gary R. Cutter, PhD,** has disclosed serving on the data/safety monitoring committees for AstraZeneca, Avexis Pharmaceuticals, BioLineRx, BrainStorm Cell Therapeutics, Bristol Myers Squibb/Celgene, CSL Behring, Galmed, Green Valley Pharma, Mapi Pharmaceuticals, Merck, Merck/Pfizer, Mitsubishi Tanabe, OPKO Biologics, Neurim, Novartis, Orphazyme, Sanofi, Reata, Teva, Viela Bio, the National Heart, Lung, and Blood Institute (Protocol Review Committee), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Obstetric-Fetal Pharmacology Research Unit Oversight Committee); serving on consulting/advisory boards for Alexion, Antisense Therapeutics, Biodelivery Sciences International, Biogen, Clinical Trial Solutions LLC, Genzyme, Genentech, GW Pharmaceuticals, Immunic, Klein Buendel, MedImmune/Viela Bio, MedDay, Merck/Serono, Neurogenesis Ltd, Novartis, Osmotica, Perception Neuroscience, Protolix Biotherapeutics, Recursion/Cerexis Pharmaceuticals, Regeneron, Reckover Pharmaceuticals, Roche, SAB Biotherapeutics, and TG Therapeutics; and being president of Pythagoras, Inc, a private consulting company. **Robert J. Fox, MD, MSc,** has disclosed receiving consulting fees from AB Science, Biogen, Celgene, EMD Serono, Genentech, Genzyme, Immunic, Janssen, Novartis, Sanofi, and TG Therapeutics; research funding from Biogen, Novartis, and Sanofi; and royalties from Demos Publishing. **Timothy Vollmer, MD,** has disclosed receiving compensation for lectures and consultancy from Biogen, Genentech/Roche, Viela Bio, Celgene, EMD Serono, and Novartis; and research support from Rocky Mountain Multiple Sclerosis Center, Celgene, Biogen, Anokion, Genentech, F. Hoffmann-La Roche Ltd, GW Pharmaceuticals, and TG Therapeutics Inc. **Tuula Tyry, PhD,** has disclosed no relevant financial relationships. **Amber Salter, PhD,** has disclosed serving as a statistical editor for *Circulation: Cardiovascular Imaging*. The staff at IJMSC, CMSC, and Delaware Media Group who are in a position to influence content have disclosed no relevant financial relationships. **Laurie Scudder, DNP, NP,** Continuing Education Director CMSC, has served as Reviewer for this activity. She has disclosed no relevant financial relationships. One peer reviewer for IJMSC has disclosed relationships with Alexion (consulting fee, speakers' bureau); Biogen, Bristol Myers Squibb, EMD Serono, Genentech (consulting fee, speakers' bureau, contracted research); Celgene, Novartis, Sanofi Genzyme (consulting fee, contracted research); Viela Bio (consulting fee); National MS Society, PCORI, Atara Biotherapeutics, Roche (contracted research); and Taro Pharmaceuticals, AstraZeneca, Pfizer, Johnson & Johnson, Inovio, GlaxoSmithKline, Viatris, Gilead, Altimmune Inc, CytoDyn Inc (ownership interest

DOI: 10.7224/1537-2073.2020-133

[common stocks]). The other peer reviewer has disclosed relationships with Celgene (speakers' bureau, contracted research); and Merck, EMD Serono, Roche, AbbVie (contracted research). *Note:* Financial relationships may have changed in the interval between listing these disclosures and publication of the article.

Method of Participation:
Release Date: December 1, 2021
Valid for Credit Through: December 1, 2022

In order to receive CME/NCPD/CPE credit, participants must:
1) Review the continuing education information, including learning objectives and author disclosures.
2) Study the educational content.
3) Complete the post-test and evaluation, which are available at https://www.highmarksce.com/mscare.

Statements of Credit are awarded upon successful completion of the evaluation and the post-test with a passing score of >70%. The post-test may be retaken if necessary. There is no fee to participate in this activity.

Disclosure of Unlabeled Use: This educational activity may contain discussion of published and/or investigational uses of agents that are not approved by the FDA. The CMSC and Delaware Media Group do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the CMSC or Delaware Media Group.

Disclaimer: Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any medications, diagnostic procedures, or treatments discussed in this publication should not be used by clinicians or other health care professionals without first evaluating their patients' conditions, considering possible contraindications or risks, reviewing any applicable manufacturer's product information, and comparing any therapeutic approach with the recommendations of other authorities.

Observational studies and registries can play a critical role in elucidating the natural and treated history of multiple sclerosis (MS) and identifying factors associated with outcomes such as disability and health-related quality of life. The North American Research Committee on Multiple Sclerosis (NARCOMS) Registry is one of multiple registries worldwide that focuses on people with MS, but one of the very few patient-driven MS registries. On the 25th anniversary of the first data collection for the NARCOMS Registry, we discuss the importance of disease registries in the MS field, describe key concepts related to registry design and management, and highlight findings from MS registries relevant to clinical care or health policy. *Int J MS Care.* 2021;23:276-284.

Multiple sclerosis (MS) is a complex chronic disease, the etiology of which remains incompletely understood. Similar to disease etiology, factors that influence outcomes and many aspects of the MS disease experience are also incompletely understood. Observational studies and registries can play a critical role in elucidating these issues. The North American Research Committee on Multiple Sclerosis (NARCOMS) Registry is one of multiple registries worldwide that focus on people with MS,[1] but one of the very few patient-driven MS registries. With operational support and funding from the Consortium of Multiple Sclerosis Centers (CMSC), the NARCOMS Registry project was initiated in 1993 under the leadership of Dr Timothy Vollmer. Data collection began in 1996 as part of the Yale MS Patient Registry and now is an ongoing project of the CMSC. Enrollment involves people with MS completing a questionnaire online or mailing it to the Registry Coordinating Center. Initially, data collection occurred only at enrollment, but longitudinal semiannual data collection began in January 2000. To date, more than 41,000 participants have enrolled in the NARCOMS Registry, contributing data to at least 140 peer-reviewed publications.

Herein, on the 25th anniversary of the first data collection for the NARCOMS Registry, we discuss the importance of disease registries in the MS field, describe key concepts related to registry design, and highlight findings from MS registries relevant to clinical care and health policy. We illustrate these concepts and findings using salient examples predominantly from the NARCOMS Registry. Characteristics of several MS registries are reviewed elsewhere.[2]

Why Are Registries Needed?

Several studies have highlighted the high burden of neurologic disorders worldwide. The Global Burden

From the Department of Internal Medicine and Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada (RAM); Department of Biostatistics, University of Alabama at Birmingham, Birmingham, AL, USA (GRC); Mellen Center for Multiple Sclerosis, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA (RJF); Department of Neurology, Rocky Mountain Multiple Sclerosis Center at Anschutz Medical Campus, University of Colorado Denver, Denver, CO, USA (TV); Phoenix, AZ, USA (TT); and Division of Biostatistics, Washington University in St Louis, St Louis, MO, USA (AS [now at UT Southwestern Medical Center]). *Correspondence:* Ruth Ann Marrie, MD, PhD, Health Sciences Centre, GF 543, 820 Sherbrook St, Winnipeg, MB R3A 1R9, Canada; e-mail: rmarrie@hsc.mb.ca.

of Disease Study reported that in 2016 neurologic disorders were the leading cause of disability-adjusted life years, which reflect the combined effects of years of life lost and years lived with disability.[3] That year, an estimated 18,932 deaths and 1,151,478 disability-adjusted life years were attributed to MS.[4] Despite the adverse impact of MS and other neurologic disorders on affected individuals, their families, society, and health systems, critical gaps in our knowledge of these disorders persist. The 2020 *Atlas of MS* highlighted persistent gaps in knowledge regarding the incidence and prevalence of MS worldwide.[5] The heterogeneity of MS outcomes, including treatment responses, remains incompletely understood.[6] Clinical trials provide information about the effectiveness of therapies used under controlled conditions, but clinical trial populations often differ from populations managed in general clinical practice with respect to age, comorbidity burden, and other characteristics.[7] Thus, the effectiveness, safety, and tolerability of therapies tested in clinical trials when applied in clinical populations are uncertain. Registries are one key way to fill these knowledge gaps to better inform clinical care and health policy. A systematic review of 17 studies found that clinical quality registries were associated with improved processes of care and outcomes.[8]

What Are Registries?

Registries are collections of information about individuals. They may be classified by their focus on 1) exposure to a particular disease or condition, such as MS; 2) exposure to a health care product, such as a device or drug; or 3) exposure to a particular health care service.[9] Registries collect health status information using consistent observational (noninterventional) study approaches, although some registries may collect information after a specific intervention. Compared with other sources of real-world data, such as administrative databases or electronic medical records, registries have several strengths,[10] including uniform data collection according to standard data definitions, the opportunity to collect long-term outcomes, and more comprehensive clinical data than may be obtained from administrative (health claims) data. They may also capture patient-reported outcomes (PROs). However, registries also face challenges related to sustainability, the potential for selection bias, and the need to monitor and maintain data quality.

The purpose of a registry should be defined explicitly before it is designed to ensure that the data collected will be appropriate for that purpose. Patient registries may be used to understand the natural and treated history of disease and prognostic factors; to understand disease treatment; to explore outcomes such as employment, socialization, and disparities in care; to measure quality of care; or to monitor treatment safety and harm.

The vision of the NARCOMS Registry is to improve clinical care and quality of life for persons with MS and their families through increased knowledge about MS. The mission of NARCOMS is to conduct epidemiological and health services research in MS; and to support new investigators and facilitate exploration of emerging research areas, as well as to participate in collaborative multicenter research focused in MS on its treatment and prevention. The goals of the NARCOMS Registry are to increase the understanding of MS from the perspective of the person with MS, to assess knowledge of treatment and health care services, and to disseminate knowledge and increase awareness of MS and its management to patients, their families, care providers, researchers, advocacy groups, and policy makers. The mission, vision, and goals of the NARCOMS Registry guide what data are collected and what projects are supported. As discussed further herein, the emphasis on the patient perspective underlies the focus on collecting data directly from the participant rather than from clinicians.

What Are the Important Design Issues for Registries?

Several critical issues should be considered when designing a registry. Legal and ethical issues may be particularly challenging. Presently, the NARCOMS Registry is approved by the institutional review board of Washington University in St Louis. Participants agree that their deidentified information may be used for research purposes and to be contacted regarding studies for which they may be eligible. Detailed discussions of legal and ethical issues can be found elsewhere.[10,11] NARCOMS Registry participants agree to the use of their information for research purposes. Each survey receives institutional review board approval. Other important issues include the approach to recruitment and retention, data release procedures, and standard operating procedures; these are reviewed elsewhere.[12,13] Depending on the purpose of the registry, the target population, the type of information to be collected, and the method of data collection will differ.

Target Population

The target population refers to the population to whom the registry findings are intended to be applied.[14] A population-based registry aims to capture all potential participants in a given population, for example,[15] all adults with MS in the United States. A population-based

design is necessary for estimating the incidence of disease or for examining etiologic factors. A 2017 review of neurodegenerative disease registries highlighted several common sources of potential bias when registries are not population-based, such as inclusion of misdiagnosed cases, subtle changes in the types of cases included over time, failure to capture minority or disadvantaged populations, a skewed characterization of disease phenotype, as well as period and cohort effects.[15]

Registries that are not population-based can still address important questions, such as health outcomes, but assessing the generalizability of the registry population remains important to widespread applicability of the findings. The NARCOMS Registry is open to people with MS living anywhere in the world, although most participants reside in the United States. The Registry is not population-based. As part of the national MS Surveillance Registry feasibility project commissioned by the Agency for Toxic Substances and Disease Registry, the overlap was examined between participants in the NARCOMS Registry diagnosed before 2006 and persons captured in the Veterans Health Administration database, Veterans Benefits Administration database, and Medicare databases in Minnesota, Georgia, and South Carolina from 2001 to 2005.[16] Overall, 28.8% of 1855 NARCOMS Registry participants were captured in the administrative data sets. However, 90.2% of NARCOMS Registry participants who reported having Medicare coverage were identified in that database. Similarly, 66% of NARCOMS Registry participants who reported that they were veterans were captured in the Veterans Health Administration or Veterans Benefits Administration database. Overall, one-quarter of NARCOMS Registry participants were not identified in any of the administrative data sources. This highlights the difficulty of capturing individuals with MS solely using administrative data in the United States and the consequent value of registries.

Data Collection Approaches

Registries may be broadly classified as clinician-driven or patient-driven. In a clinician-driven registry, the clinician is responsible for participant recruitment and data collection. A substantial proportion of MS registries are clinician-driven, including the New York State Multiple Sclerosis Consortium and the Veterans Affairs Multiple Sclerosis Surveillance Registry.[17-19] Clinician-driven registries have several potential benefits. Engagement of clinicians enhances participant consent rates and recruitment of sufficient samples and helps ensure that participant diagnoses are accurate. However, these registries often lack the patient perspective, and data quality may suffer if the data collection burden on clinicians is high. The burden may be mitigated by integrating data collection with clinical care through electronic health records (see Box 1 for a description of the MS Surveillance Registry developed in the Veterans Health Administration).

In contrast, the NARCOMS Registry and iConquerMS are patient-driven registries. Patient-driven registries have the advantage of easily crossing geographic and jurisdictional boundaries[20] and may be more cost-effective than clinician-driven registries. Selection bias is a potential concern due to the recruitment methods used and the inability to explicitly contact all eligible persons in the region or regions covered by the registry. For example, patient-driven registries typically rely on internet access and may miss individuals without such access or who use it infrequently; however recent studies suggest this may not be a major concern.[21] Recruitment sources for the NARCOMS Registry include the CMSC and clinician offices, the National Multiple Sclerosis Society, the internet, *NARCOMS Now* magazine, and traditional media. The NARCOMS Registry offers recruitment materials to clinicians to support discussions about accessible opportunities to engage in meaningful research that has the potential to inform clinical practice. The addition of alternative methods of participation also mitigates potential biases in patient-driven registries. To address this issue, the NARCOMS Registry

Box 1. An example of an integrated registry in multiple sclerosis (MS)

What is the Multiple Sclerosis Surveillance Registry (MSSR)?
The MSSR is an MS registry focused on veterans with MS with the primary goal of optimizing their care.

How are the data collected?
- For each patient encounter, clinicians provide clinical information using the MS Assessment Tool, which can be accessed from the patient's health record or from an online portal. This tool standardizes data collection and requires 5-15 minutes to complete.
- Data from other sources, including health care utilization files, pharmacy, prosthetics, laboratory, and radiology databases, are also integrated into the MSSR.

What are the implementation issues?
- Clinicians need to change workflow.
- Some information relevant to clinical care and research, such as neurologist-determined relapse occurrence and Expanded Disability Status Scale score, is not currently captured.
- A partnership between clinicians and information technology teams was needed.

[a]maelstrom-research.org/mica/individual-study/mssr

offers participants the option to complete questionnaires either online or on paper by registering at narcoms.org/participate. On average, 60% of participants opt to complete semiannual questionnaires online. It may be harder to retain participants long-term when there is no direct engagement of clinicians. For example, attrition is a greater problem in internet-delivered interventions than in face-to-face interventions.[22] Concerns about data quality may also be raised because the data are not verified by a clinician or data manager at the site of interaction.

In 2005, recognizing the importance of the accuracy of MS diagnosis for the NARCOMS Registry, we compared self-reported diagnoses of Registry participants with physician-reported diagnoses and with diagnoses based on medical records review.[23] We randomly sampled 240 participants, of whom 109 were considered to be active in the Registry and had current contact information. Of the 109 participants, 52 consented, 29 refused, and 28 did not respond, for a mean ± SD weighted response rate of 76.3% ± 4.5%. For each respondent we conducted interviews, requested medical records, and surveyed their treating physicians when possible. Based on these three modalities, we confirmed a diagnosis of MS in a mean ± SD of 98.7% ± 1.3% of respondents, supporting the validity of the diagnoses reported by NARCOMS Registry participants. In addition to requesting medical record review or confirmation of diagnosis by a treating clinician, other strategies to increase confidence in self-reported diagnoses include capturing additional information regarding medication history or disease characteristics[23] and linkage (with consent) to other data sources, such as administrative health claims data.[24]

Types of Data Collected

Broadly, registries may collect clinician-reported data, performance-based data, and patient-reported data. Clinician-driven registries tend to capture the first two types of data, and patient-driven registries tend to capture the last. It is uncommon for all three types of data to be collected in a single registry, although the MS Partners Advancing Technology and Health Solutions (MS PATHS) study aims to do so.[25] The MS PATHS is an initiative collecting clinician-reported, performance-based, magnetic resonance imaging, and patient-reported data at ten participating MS clinics in three countries. The data are used to facilitate clinical care and for research.

Clinician-reported data commonly include diagnosis, disability status as assessed on neurologic examination (eg, using the Expanded Disability Status Scale[26]), relapses, and use of disease-modifying therapy. Performance-based measures provide a standardized means of assessing functional abilities, distinct from what the clinician assesses or the perceived performance of the participant. The Timed 25-Foot Walk test is one such measure.[27] Patient-reported data may encompass a broad range of information, including sociodemographic characteristics, health services use, and PROs (see Table 1 for the core data elements captured in the NARCOMS Registry, and see https://www.maelstrom-research.org/mica/individual-study/narcoms for access to detailed metadata).

The PROs capture information that can be assessed only from the perspective of the patient, such as health-related quality of life, pain, and fatigue. As such, PROs are highly relevant to people with MS. By design, PROs are collected directly from the patient and do not involve interpretation by or the influence of any person other than the patient. More than 80 MS-specific PROs have been developed, and many generic PROs also have been used in studies of MS.[29] The NARCOMS Registry routinely captures disability status and health-related quality of life.

What Are the Data Quality and Management Issues?

Good data quality is essential to the utility of a registry and to the validity of conclusions that can be drawn from the data. Multiple factors may contribute to poor data quality, and they may be broadly classified as systematic or random.[30] Common systematic causes of data errors in disease registries include ambiguous data definitions, unclear data collection guidelines, poorly designed data collection instruments, programming errors, lack of a data dictionary available for those collecting data, and lack of a plan for quality improvement. Thus, achieving a high degree of data quality requires an ongoing consistent approach to data collection, with user-friendly data collection forms and standardized definitions that are readily accessible to investigators and data collectors.[30] Implementation of automatic data validation rules at the time of data entry can also be helpful. Where applicable, the training and auditing of data collectors is critical. Data quality should be evaluated routinely, and a plan to correct inaccurate data if appropriate and fill in incomplete data should be constructed. MSBase, for example, has developed a standardized process to evaluate data quality, including an assessment of completeness, the proportion of variables with recorded values corresponding to their true range, consistency of the findings across

Table 1. Examples of data elements collected by NARCOMS Registry[a]

Category	Specific elements
Sociodemographic information	Date of birth Gender Race/ethnicity Annual household income Highest level of education reached Marital status Health insurance status Employment status
Clinical characteristics/ outcomes	Age at MS symptom onset Age at MS diagnosis Disability/symptom impact (measured using Patient-Determined Disease Steps and SymptoMScreen[28] depending on year) Clinical course Relapses in past 6 months Comorbid conditions Health-related quality of life (measured using RAND-12 and Health Utilities Index–Mark III depending on year)
Health behaviors	Smoking Physical activity Height and weight
Health care services	Use of emergency departments Visits to health care providers Hospitalizations
Treatment	Use of disease-modifying therapies (name, period of use) Use of symptomatic therapies (not on every survey)
Special topics[b]	Preferences regarding physician assistance in dying Bone health Diet Health literacy Use of assistive devices Health information sources Bowel and bladder function Trigeminal neuralgia Visual functioning Vertigo

Abbreviation: NARCOMS, North American Research Committee on Multiple Sclerosis.
[a]More information may be found at maelstrom-research.org/mica/individual-study/narcoms.
[b]Selected examples.

variables, and believability.[31] MSBase also assesses data density and generalizability of the study population with respect to the known epidemiology of MS.

The NARCOMS Registry has made extensive efforts to validate key data elements and measures or to use measures for which the validity and reliability are already established. For example, in a sample of 32 participants, we measured simple percentage agreement between patient- and physician-reported year of diagnosis.[32] For year of diagnosis, agreement was exact for 17 of 32 participants (53.1%), within 1 year for 20 of 32 (62.5%), and within 2 years for 25 of 32 (78.1%). The test-retest reliability of participant-reported year of MS diagnosis was high, with an intraclass correlation coefficient of 0.99. Findings were similar for year of MS symptom onset (intraclass correlation coefficient = 0.90). Disability status is reported using Patient-Determined Disease Steps, an ordinal measure that correlates strongly with a physician-scored Expanded Disability Status Scale score, distance reached during the Six-Minute Walk Test, and 12-item Multiple Sclerosis Walking Scale score.[33] Comorbidity is assessed using a validated questionnaire.[34] For that questionnaire, agreement between self-reported comorbid conditions and medical records was high ($\kappa > 0.82$) for diabetes and hypertension; substantial ($\kappa = 0.62$-0.80) for hyperlipidemia, thyroid disease, glaucoma, and lung disease; and moderate ($\kappa = 0.43$-0.56) for osteoporosis, irritable bowel syndrome, migraine, depression, heart disease, and anxiety disorders.

Registry management is resource intensive, which can challenge sustainability. Registries require ongoing engagement by clinicians or participants (with MS), regular communication with stakeholders, data collection and management systems, a data management team, and financial support for these infrastructure costs.[13] For example, the NARCOMS Registry distributes the *NARCOMS Now* magazine to Registry participants to maintain engagement and share research findings from the NARCOMS Registry to which participants have contributed as well as other information of potential interest. The NARCOMS Registry has a formal data coordinating center for data management, and data are collected and managed using REDCap (Research Electronic Data Capture),[35] a secure Web-based application that can be compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the General Data Protection Regulation. The specifics of where and how the data will be stored should be established at the outset. Organizational, physical, and technological safeguards can be used to protect the confidentiality and security of the data collected.

Currently, the NARCOMS Registry is housed at Washington University in St Louis. Initially the NARCOMS Registry was established at Yale University, and during its 25-year history it has moved to Phoenix, Arizona; Denver, Colorado; and Birmingham, Alabama, before reaching its current location. Some registries are funded by a parent organization (eg, foundation

or government), which requires continued commitment by the parent organization to provide funding. For example, the French Multiple Sclerosis Registry (Observatoire Français de la Sclérose en Plaques [OFSEP]; clinicaltrials.gov identifier NCT02889965) has primarily been funded by the French government.[36] Others use access fees to offset the cost of the requested analysis and ongoing operational costs. Philanthropy can also be an important source of funding. The NARCOMS Registry uses a combination of these funding approaches. Specifically, the NARCOMS Registry receives partial funding of operational costs from the CMSC. Other funding comes from academic and nonacademic/industry researchers requesting access to existing deidentified data or requesting collection of new data (see https://www.narcoms.org/researchers-providers for access details).

How Have MS Registries Informed Our Understanding of MS?

Globally, MS registries have contributed substantially to our understanding of MS. Previous reviews have summarized contributions by the Danish MS Registry and MSBase.[17,37] Broadly, registries have provided information regarding the incidence of MS and risk factors, characterized disease progression over time, and assessed the impact of disease-modifying therapy and the comparative effectiveness of different disease-modifying therapies.[19,37,38] MSBase, for example, showed that the strongest predictor of postpartum relapses in MS is the presence of prepartum relapses.[39] The Danish MS Registry showed that switching to highly effective therapy rather than moderately effective therapy after a relapse is associated with a subsequently lower annualized relapse rate.[40]

The NARCOMS Registry has also informed our understanding of MS. For example, lower socioeconomic status is associated with greater disability among persons with MS, and lower socioeconomic status accounts for some of the racial disparities in disease severity observed in MS.[41] Vascular comorbidity, including hypertension, hyperlipidemia, disability, and heart disease, is also associated with accelerated disability progression.[42] Diet is associated with symptom severity; that is, a healthy diet is associated with lower odds of reporting severe fatigue, depression, and pain.[43]

Future Directions: Enhancing the Impact of Registries

Registries have made an important contribution to our understanding of MS, but multiple registries exist worldwide with different goals. A key question is how to make the best use of these registries given the resources that are required to sustain them. In 2016, Bebo et al[2] provided an overview of major registries and ongoing cohort studies in the MS field with the goal of making recommendations to enhance their impact. Those recommendations included 1) create a federated network of cohorts; 2) standardize data collection and management; 3) identify and prioritize research questions; 4) encourage collection of physician-reported outcomes and PROs; 5) encourage technological innovation; 6) develop a universal informed consent process; and 7) provide sustainable funding.

Subsequently, the International Advisory Committee on Clinical Trials in Multiple Sclerosis made recommendations to improve the quality of real-world evidence for informing our understanding of MS and its treatments. Some of the recommendations extend those made by Bebo et al[2] by focusing on specific actions that would allow real-world data collected through registries and other data sources to be used and combined more effectively.[10] These included developing a metadata catalog of existing cohorts and registries, developing standards to facilitate data exchange, developing guidelines to aid data harmonization in MS, and developing a toolkit that could support the development of high-quality registries and other observational studies by providing information regarding ethics and privacy issues, standard informed consent language, and standard operating procedures for data collection.

The MS Metadata Collective is a metadata catalog being developed for North American registries and cohort studies in MS with the support of Maelstrom Research (see maelstrom-research.org/network/msmdc).[44] It includes information regarding the NARCOMS Registry and 12 other studies. Metadata catalogs are discussed in more detail by Geys et al in this issue of IJMSC.[45] Further expansion of metadata catalogs can enhance the visibility of registries (ie, their findability) and enhance opportunities for collaborative and comparative work.

Although it is still in development, the Multiple Sclerosis Metadata Collective provides the opportunity to identify similarities and differences in the types of variables collected as to whether different instruments are used to measure the same underlying construct, such as pain or fatigue. Because multiple differences exist, data harmonization will be an important step to support collaborative work between registries. Harmonization can enhance the comparability of similar measures across studies to ease joint analysis.[46] When data have already

been collected, this process is referred to as retrospective harmonization, and the Maelstrom Research guidelines offer an approach to achieving it.[47] The Big MS Data Network has assessed the feasibility of retrospective data harmonization across five MS registries, including MSBase, OFSEP, and the Swedish, Danish, and Italian MS registries.[48] The NARCOMS Registry collaborated with the UK MS Register and the German MS Register to illustrate the feasibility of data harmonization across registries. Specifically, the three registries applied the Maelstrom Research guidelines to collaboratively evaluate employment status.[49] The NARCOMS Registry also applied existing methods to illustrate the feasibility of developing crosswalks between different instruments that assess common underlying constructs. Specifically, the NARCOMS Registry developed a crosswalk between two instruments that measure health-related quality of life: the Health Utilities Index–Mark III version and the RAND-12.[50]

Individual registries cannot capture all information necessary to answer all research questions of interest. Linkage of registry data to other data sources is a means of reducing direct data collection burden, expanding the scope of questions that can be answered, and enhancing registry impact.[24] Potentially linkable data sources include administrative (health claims) data, census data, and imaging and laboratory data. Multiple MS studies have linked registries with administrative health data.[51,52] In 2015-2016, the NARCOMS Registry conducted a study in collaboration with IQVIA to test the feasibility of linking patient-reported data from the NARCOMS Registry to health claims data.[53] Of 1000 registry participants approached, 769 (76.9%) consented to data linkage. Linkage to open medical claims and prescription claims data was achieved for 698 participants (91%) using IQVIA's HIPAA-compliant encryption engine. These findings supported the feasibility of data linkage between the NARCOMS Registry and health claims data.

PRACTICE POINTS

- Registries are collections of information about individuals. The information can be provided by the individual or a clinician, or it may be directly from electronic data sources.
- Important design issues for registries include the target population, type of information to be collected, and data collection approach (see examples at maelstrom-research.org/network/msmdc).
- Registries have informed the understanding of the epidemiology of MS and its treatments. For example, they have characterized disease progression over time and established the comparative effectiveness of different disease-modifying therapies.

Conclusions

Registries offer an important means of enhancing our understanding of chronic diseases such as MS, which is a complex and heterogeneous disease. Multiple MS registries exist worldwide and have provided important insights into the epidemiology and outcomes of the disease, supported comparative effectiveness studies, and provided valuable patient perspectives. Efforts are growing to support collaborations across registries and data linkage to further enhance our understanding of MS. □

Financial Disclosures: Dr Marrie is a co-investigator on a study funded by Biogen and Roche. Dr Cutter serves on the data/safety monitoring committees for AstraZeneca, Avexis Pharmaceuticals, BioLineRx, BrainStorm Cell Therapeutics, Bristol Myers Squibb/Celgene, CSL Behring, Galmed, Green Valley Pharma, Mapi Pharmaceuticals, Merck, Merck/Pfizer, Mitsubishi Tanabe, OPKO Biologics, Neurim, Novartis, Orphazyme, Sanofi, Reata, Teva, Viela Bio, the National Heart, Lung, and Blood Institute (Protocol Review Committee), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (Obstetric-Fetal Pharmacology Research Unit Oversight Committee); serves on consulting/advisory boards for Alexion, Antisense Therapeutics, Biodelivery Sciences International, Biogen, Clinical Trial Solutions LLC, Genzyme, Genentech, GW Pharmaceuticals, Immunic, Klein Buendel, MedImmune/Viela Bio, MedDay, Merck/Serono, Neurogenesis Ltd, Novartis, Osmotica, Perception Neuroscience, Protolix Biotherapeutics, Recursion/Cerexis Pharmaceuticals, Regeneron, Reckover Pharmaceuticals, Roche, SAB Biotherapeutics, and TG Therapeutics; and is president of Pythagoras, Inc, a private consulting company. Dr Fox has received consulting fees from AB Science, Biogen, Celgene, EMD Serono, Genentech, Genzyme, Immunic, Janssen, Novartis, Sanofi, and TG Therapeutics; research funding from Biogen, Novartis, and Sanofi; and royalties from Demos Publishing. Dr Vollmer received compensation for lectures and consultancy from Biogen, Genentech/Roche, Viela Bio, Celgene, EMD Serono, and Novartis and received research support from Rocky Mountain Multiple Sclerosis Center, Celgene, Biogen, Anokion, Genentech, F. Hoffmann-La Roche Ltd, GW Pharmaceuticals, and TG Therapeutics Inc. Dr Salter serves as a statistical editor for *Circulation: Cardiovascular Imaging*. Dr Tyry declares no conflicts of interest.

Funding/Support: Dr Marrie is supported by the Waugh Family Chair in Multiple Sclerosis and a Manitoba Research Chair. The NARCOMS Registry is a project of the CMSC.

References

1. Flachenecker P, Buckow K, Pugliatti M, et al. Multiple sclerosis registries in Europe: results of a systematic survey. *Mult Scler*. 2014;20:1523-1532.
2. Bebo BF, Fox RJ, Lee K, Utz U, Thompson AJ. Landscape of MS patient cohorts and registries: recommendations for maximizing impact. *Mult Scler*. 2018;24:579-586.

3. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18:459-480.
4. GBD 2016 Multiple Sclerosis Collaborators. Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18:269-285.
5. King R. *Atlas of MS: Mapping Multiple Sclerosis Around the World.* 3rd ed. Multiple Sclerosis International Federation; 2020.
6. Chiu AW, Richert N, Ehrmantraut M, et al. Heterogeneity in response to interferon beta in patients with multiple sclerosis: a 3-year monthly imaging study. *Arch Neurol.* 2009;66:39-43.
7. Marrie RA, Miller A, Sormani MP, et al. The challenge of comorbidity in clinical trials for multiple sclerosis. *Neurology.* 2016;86: 1437-1445.
8. Hoque DME, Kumari V, Hoque M, Ruseckaite R, Romero L, Evans SM. Impact of clinical registries on quality of patient care and clinical outcomes: a systematic review. *PLoS One.* 2017;12:e0183667.
9. Gliklich R, Dreyer NA, Leavy M. *Registries for Evaluating Patient Outcomes: A User's Guide.* 3rd ed. Agency for Healthcare Research and Quality; 2014. AHRQ publication 13(14)-EHC111.
10. Cohen JA, Trojano M, Mowry EM, Uitdehaag BM, Reingold SC, Marrie RA. Leveraging real-world data to investigate multiple sclerosis disease behavior, prognosis, and treatment. *Mult Scler.* 2020;26: 23-37.
11. Hogan DB, Warner J, Patten S, et al. Ethical and legal considerations for Canadian registries. *Can J Neurol Sci.* 2013;40(suppl 2):S5-S22.
12. Hamilton M, Genge A, Johnston M, et al. Patient recruitment by neurological registries. *Can J Neurol Sci.* 2013;40(suppl 2):S23-S26.
13. Johnston M, Campbell C, Hayward R, et al. Registry data storage and curation. *Can J Neurol Sci.* 2013;40(suppl 2):S35-S40.
14. Glicklich R, Dreyer N, Leavy M, eds. *Registries for Evaluating Patient Outcomes: A User's Guide.* 3rd ed. Agency for Healthcare Research and Quality; 2014. AHRQ publication 13(14)-EHC111.
15. Rooney JPK, Brayne C, Tobin K, Logroscino G, Glymour MM, Hardiman O. Benefits, pitfalls, and future design of population-based registers in neurodegenerative disease. *Neurology.* 2017;88: 2321-2329.
16. Tyry T, Salter A, Cutter G, Wu J, Horton K, Antao V. Role of self-report registries in developing a national multiple sclerosis (MS) surveillance system: promising results from the NARCOMS database. Paper presented at: American Public Health Association Annual Meeting; October 21-31, 2012; San Francisco, CA.
17. Kalincik T, Butzkueven H. The MSBase registry: informing clinical practice. *Mult Scler.* 2019;25:1828-1834.
18. Wallin MT, Whitham R, Maloni H, et al. The Multiple Sclerosis Surveillance Registry: a novel interactive database within the Veterans Health Administration. *Fed Pract.* 2020;37(suppl 1):S18-S23.
19. Jacobs LD, Wende KE, Brownscheidle CM, et al. A profile of multiple sclerosis: the New York State Multiple Sclerosis Consortium. *Mult Scler.* 1999;5:369-376.
20. Rhodes SD, Bowie DA, Hergenrather KC. Collecting behavioural data using the world wide web: considerations for researchers. *J Epidemiol Community Health.* 2003;57:68-73.
21. Gupta S, Bayoumi AM, Faughnan ME. Rare lung disease research: strategies for improving identification and recruitment of research participants. *Chest.* 2011;140:1123-1129.
22. Geraghty AWA, Torres LD, Leykin Y, Pérez-Stable EJ, Muñoz RF. Understanding attrition from international internet health interventions: a step towards global eHealth. *Health Promot Int.* 2012;28:442-452.
23. Marrie RA. *The Influence of Comorbid Diseases and Health Behaviors on Clinical Characteristics, Disability at Diagnosis and Disability Progression in Multiple Sclerosis.* Dissertation. Epidemiology and Biostatistics, Case Western Reserve University; 2007.
24. Jette N, Atwood K, Hamilton M, et al. Linkage between neurological registry data and administrative data. *Can J Neurol Sci.* 2013;40(suppl 2):S32-S34.
25. Mowry EM, Bermel RA, Williams JR, et al. Harnessing real-world data to inform decision-making: Multiple Sclerosis Partners Advancing Technology and Health Solutions (MS PATHS). *Front Neurol.* 2020;11:632.
26. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology.* 1983;33: 1444-1452.
27. Motl RW, Cohen JA, Benedict R, et al. Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. *Mult Scler.* 2017;23:704-710.
28. Fitzgerald KC, Salter A, Tyry T, et al. Validation of the SymptoMScreen with performance-based or clinician-assessed outcomes. *Mult Scler Relat Disord.* 2019;29:86-93.
29. Khurana V, Sharma H, Afroz N, Callan A, Medin J. Patient-reported outcomes in multiple sclerosis: a systematic comparison of available measures. *Eur J Neurol.* 2017;24:1099-1107.
30. Arts DGT, De Keizer NF, Scheffer G-J. Defining and improving data quality in medical registries: a literature review, case study, and generic framework. *J Am Med Inform Assoc.* 2002;9:600-611.
31. Kalincik T, Kuhle J, Pucci E, et al. Data quality evaluation for observational multiple sclerosis registries. *Mult Scler.* 2017;23: 647-655.
32. Marrie RA, Cutter G, Tyry T, Campagnolo D, Vollmer T. Validation of the NARCOMS Registry: diagnosis. *Mult Scler.* 2007;13:770-775.
33. Learmonth YC, Motl RW, Sandroff BM, Pula JH, Cadavid D. Validation of Patient Determined Disease Steps (PDDS) scale scores in persons with multiple sclerosis. *BMC Neurol.* 2013;13:37.
34. Horton M, Rudick RA, Hara-Cleaver C, Marrie RA. Validation of a self-report comorbidity questionnaire for multiple sclerosis. *Neuroepidemiology.* 2010;35:83-90.
35. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research Electronic Data Capture (REDCap): a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42:377-381.
36. Vukusic S, Casey R, Rollot F, et al. Observatoire Français de la Sclérose en Plaques (OFSEP): a unique multimodal nationwide MS registry in France. *Mult Scler.* 2020;26:118-122.
37. Koch-Henriksen N, Stenager E, Laursen B. The use of epidemiological multiple sclerosis registers in research: the Danish MS Registry. *Acta Neurol Scand Suppl.* 2012;195:7-12.
38. Granqvist M, Burman J, Gunnarsson M, et al. Comparative effectiveness of dimethyl fumarate as the initial and secondary treatment for MS. *Mult Scler.* 2020;26:1532-1539.
39. Hughes SE, Spelman T, Gray OM, et al. Predictors and dynamics of postpartum relapses in women with multiple sclerosis. *Mul Scler.* 2014;20:739-746.
40. Chalmer TA, Kalincik T, Laursen B, et al. Treatment escalation leads to fewer relapses compared with switching to another moderately effective therapy. *J Neurol.* 2019;266:306-315.
41. Marrie RA, Cutter G, Tyry T, Vollmer T, Campagnolo D. Does multiple sclerosis-associated disability differ between races? *Neurology.* 2006;66:1235-1240.
42. Marrie RA, Rudick R, Horwitz R, et al. Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. *Neurology.* 2010;74:1041-1047.
43. Fitzgerald KC, Tyry T, Salter A, et al. Diet quality is associated with disability and symptom severity in multiple sclerosis. *Neurology.* 2018;90:e1-e11.
44. Bergeron J, Doiron D, Marcon Y, Ferretti V, Fortier I. Fostering population-based cohort data discovery: the Maelstrom Research cataloguing toolkit. *PLoS One.* 2018;13:e0200926.
45. Geys L, Parciak T, Pirmani A, et al. The Multiple Sclerosis Data Alliance Catalogue: enabling web-based discovery of metadata from real-world multiple sclerosis data sources. *Int J MS Care.* 2021;23: 261-268.
46. Magalhaes S, Wolfson C. Harmonization: a methodology for advancing research in multiple sclerosis. *Acta Neurol Scand.* 2012;126:31-35.
47. Fortier I, Raina P, Van den Heuvel ER, et al. Maelstrom Research guidelines for rigorous retrospective data harmonization. *Int J Epidemiol.* 2017;46:103-105.
48. Iaffaldano P, Butzkueven H, Hillert J, et al. Big Multiple Sclerosis Data network: data sharing among five large MS registries. http://www.ofsep.org/ECTRIMS/2017/P738_BIG%20MS%20DATA_poster1.pdf
49. Salter A, Stahmann A, Elenberger D, et al. Data harmonization for collaborative research among MS registries: a case study in employment. *Mult Scler.* 2021;27:281-289.
50. Marrie RA, Dufault B, Tyry T, Cutter GR, Fox RJ, Salter A. Developing a crosswalk between the RAND-12 and the health utilities index for multiple sclerosis. *Mult Scler.* 2020;26:1102-1110.
51. McKay KA, Tremlett H, Fisk JD, et al. Psychiatric comorbidity is associated with disability progression in multiple sclerosis. *Neurology.* 2018;90:e1316-e1323.
52. Leray E, Vukusic S, Debouverie M, et al. Excess mortality in patients with multiple sclerosis starts at 20 years from clinical onset: data from a large-scale French observational study. *PLoS One.* 2015;10:e0132033.
53. Salter A, Wada K, Burudpakdee C, et al. Linking NARCOMS, a multiple sclerosis patient registry, to US healthcare claims database: introduction a collaborative, comprehensive research database for observational studies. *Mult Scler.* 2019;25(suppl 2):165-166.