Clinical Perspective

The future of neurological patient registries

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Patient registries represent an important platform across geographical areas that can provide critical epidemiological data and information on the effectiveness of therapies or devices within a given disease group. Neurological patient registries represent an exciting opportunity to directly impact patient care and clinical trial readiness. Neurological registries also aid in the formulation of investigator networks and support translational research pipelines enhancing collaboration and cost–effectiveness of clinical research. Registries collecting high-quality data with near complete to complete ascertainment have the ability to generate useful knowledge about diseases, which is more generalizable to larger disease populations.

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The broad spectrum of patient registries & their applications

A patient registry can be defined as an observational cohort study of real-world clinical practice related to a disease condition or procedure/therapy, without a study-mandated treatment. Registries represent a valuable methodology that can catalog and track patients across geographical areas, can be used to provide epidemiological data, and can provide evidence of effectiveness of treatments and devices [1]. The range of current and future applications of neurological registries will be discussed in this article.

Registries have emerged as a useful tool for cataloging patient information across various neurological conditions. The taxonomy of registries includes product registries to track product exposures and outcomes, health services registries to track healthcare exposures (i.e., procedures) and their outcomes, as well as disease or condition registries to track participants with a chronic or temporary medical condition or disease. Registries can provide robust data on natural history of disease through consistent data collection over long periods of time. As an example, the North American Research Committee on Multiple Sclerosis Registry has collected symptom severity data of over 35,000 patients for over 15 years, providing estimates of symptom prevalence by time from symptom onset from year 0 to year 30 providing a reference for comparison of a given patient's symptoms, at a specific time point, to that of the cohort [2].

There are many examples of registries that have had a significant impact on clinical research. The Irish Motor Neurone Disease Register has demonstrated near-complete case ascertainment of amyotrophic lateral sclerosis (ALS) cases within Ireland [3]. Studies of the Irish ALS population using this registry have provided a more complete description of the cognitive and clinical characteristics of patients with ALS who carry expansions in the newly identified C9orf72 hexanucleotide repeat through combining cataloged data on genotype, demographics, family history and neuroimaging findings [4]. Clinical trial readiness has been a major focus of the Translational Research in Europe – Assessment and Treatment of Neuromuscular Diseases global patient registry for Duchenne muscular dystrophy (DMD). This registry records a detailed

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common medical data set across 31 countries including over 13,500 patients, resulting in geographic mapping of cases and trial sites with the ability to rapidly identify potential trial participants for clinical trials [5]. The Danish National Registry of Patients on the other hand has produced important epidemiological data [6]. For example, they examined trends in stroke outcomes for over the past 18 years and reported improvements in short- and long-term mortality between 1994 and 2011 with reductions in 30-day mortality of 45% for ischemic stroke and 35% for intracerebral hemorrhage [7]. Similarly, the Sagrat Cor Hospital of the Barcelona Stroke Registry reported trends in stroke outcomes by stroke subtype [8]. Stroke research has benefited from population-based registry data in several ways. Registry data have demonstrated declining incidence of ischemic stroke over time [9], elucidated stroke epidemiology [10], reported the natural history of infarctions in different vascular territories [11] and highlighted the important role of atrial fibrillation [6].

Registries & 'real world data'

A benefit of registries with very high or near-complete population ascertainment is that they are typically highly generalizable to the source population. In comparison, clinical trials, due to highly stringent eligibility criteria are often less generalizable to the overall source population. For example, Logroscino *et al.* used data from the Irish, UK and Italian population-based ALS registries to demonstrate that ALS incidence is homogenous across Europe [12].

Registries, research & regulatory activities

Clinical trials remain the gold standard methodology to demonstrate efficacy of a drug or device seeking regulatory approval. Registry data, however, are being increasingly recognized and used to supplement clinical trial data in regulatory decision-making. As the primary focus of clinical trials is to provide short-term efficacy data, registry data can provide long-term data on safety, as well as record uncommon side effects. Prospective registry studies are a component of the EMA risk-management plans and are similarly employed by the US FDA Risk Evaluation and Mitigation Strategies. A review of 29 drugs approved by both agencies demonstrated the use of prospective registries as a component of the respective risk-management plans in three (10%) of FDA and 10 (34%) of EMA approvals [13]. Use of prospective registries for postmarketing surveillance of medical devices has also been increasingly recognized as essential in assessing safety and reliability of high-risk medical devices for neurological conditions [14]. Development of expert consensus and infrastructure to support study of new devices, as they are released, has been established through the Interagency Registry for Mechanically Assisted Circulatory Support and serves as an effective example for future collaboration for neurological device monitoring [15].

Patient registries as a rigorous research methodology

Registries have emerged as a robust study design to collect prospective longitudinal data to examine the effectiveness of therapeutic agents and devices [1]. While randomized controlled trials represent the gold standard study design to examine therapeutic efficacy, registries provide valuable comparative effectiveness data where randomized controlled trials (RCTs) are not feasible. As an example, an RCT of percutaneous coronary intervention and coronary artery bypass graft in patients with one- and two-vessel coronary artery disease found that the two interventions were similarly beneficial, registry data were subsequently used to demonstrate similar benefit of percutaneous coronary intervention in patients with greater severity of disease [1,16]. Similarly, registries play an important role in postmarketing surveillance of adverse events for new and existing treatments and devices. The National Cardiovascular Data and the Carotid Artery Revascularization and Endarterectomy registries were used to compare adverse event rates of three different carotid artery stenting systems [12]. Similarly low adverse event rates were observed in 12,135 consecutive carotid stent procedures regardless of the system used over 63 months [17]. Registry-based randomized trials are emerging as novel study design combining the efficiency and large sample size of registries with the methodological rigor of RCTs by incorporating randomization and blinding into the prospective follow-up within a registry [18]. The TASTE trial was implemented within the framework of the existing Swedish Coronary Angiography and Angioplasty Registry that was already collecting much of the required patient data for the RCT. The research team rapidly identified the required subjects and completed the study of 7244 subjects at an incremental cost of US$300,000 or US$50 per subject, a cost dramatically lower than most RCTs and certainly for the sample size of subjects included [18,19].

The role of patient registries in translational research

Registries can also serve a unique role in translating benchtop research findings to the bedside. Lead compounds being translated into early human studies are generally tested in a narrow spectrum of subjects to maximize safety and minimize heterogeneity of outcome measures. Registries can serve to identify potential subjects from a larger sample through the application

of stringent inclusion and exclusion criteria. In many cases, fewer subjects would pass screening if registry prescreening were not available, increasing the time and financial burdens on these small sample size studies. For example, a genotype–phenotype analysis of Duchenne muscular dystrophy using data on 2411 subjects within the Universal Mutation Database DMD France registry identified a combination of exons potentially amenable to exon-skipping therapy in 35.4% of all DMD patients [20]. Subsequent DMD RCT efforts have included inquiries for registry data to estimate the population of DMD patients that may meet the eligibility criteria for the RCT in question through the Translational Research in Europe – Assessment and Treatment of Neuromuscular Diseases global DMD registry [5].

The emerging science of registry methodology

In the past few years, attention has begun to focus on registry methodology in an effort to enhance the design of registries, reduce costs and facilitate data comparison and analysis against data from other sources or platforms. Dreyer *et al.* published an important guide to registry development and operations that not only contains specific information for registries operating in the US but also a great deal of general theory and information applicable to registry development internationally [21]. The Canadian Neurological Registry best practice guidelines were also recently published as a supplement in *The Canadian Journal of Neurological Sciences* [22–33]. Both of these very informative resources provide a detailed approach to registry methodology ranging from development to data linkage to privacy issues.

Registry methodology, like other study designs, is contingent upon the research hypothesis or question that the operators will ask of the data. Selection of a specific methodology must meet the needs of future data analysis and quality assurance. Relevant local health data management and privacy legislation must be adhered to. In brief, registries may collect data actively through clinic-based subject recruitment, passively through online self-registration or participation can be made mandatory through legislation and provision of a waiver of consent in specific circumstances. The Registry of the Canadian Stroke Network reported the impracticability of informed consent due to a low participation rate (39.3%) resulting in important selection biases [34]. Each methodology has specific benefits and drawbacks that should be considered. For example, clinic-based data collection can be performed by trained staff using a data dictionary resulting in comparable data between collection sites but is limited by higher per-patient enrollment costs and potential gaps in patient recruitment if not all relevant clinical sites are participating. Online self-enrollment registries can miss large numbers of potential subjects if eligible subjects are not adequately made aware of the registry's existence and the accuracy and validity of self-reported data may present a concern. In all cases, a key component of a successful registry in addition to clear objectives, is clear definition of data fields (data dictionary) and practical understanding of what data can be reliably collected or reported within the chosen recruitment pathway. Some large registries, such as North American Research Committee on Multiple Sclerosis combine self-registration with validation through administrative data [35].

Supporting collaboration: registries & investigator networks

Registries are data management systems for cataloging patient clinical information. Captured clinical information can then be linked or combined with additional data such as neuroimaging, genetic or tissue samples augmenting the scope and capacity of analysis (see Figure 1). Beghi *et al.* performed a case–control study using population-based ALS registries from Italy, the UK and Ireland to examine ALS risk factors [31]. They identified physical exercise as a possible risk factor for development of ALS [36]. Kiddle *et al.*, examined 94 previously identified biomarkers for cognitive impairment in plasma samples of 677 patients from the AddNeuroMed and the Alzheimer's Research UK/Maudsley BRC Dementia Case Registry at King's Health Partners research cohorts replicating the findings for nine of the biomarkers to target in future studies [37]. Whole-exome sequencing is a novel technology facilitating gene finding in rare diseases. Campbell *et al.* performed whole-exome sequencing on family members with Familial Dilated Cardiomyopathy from the Familial Cardiomyopathy Registry and identified a single TNNT2 rare variant that segregated with the DCM phenotype in all affected relatives [38].

The best of both worlds: melding efficacy & effectiveness research

The latest opportunity for patient and device registries to contribute to clinical research also bridges the gap between rigorous clinical trial methodology and prospective observational designs, which are more generalizable. Registry-based clinical trials use preexisting registry infrastructure to perform a robust clinical trial with standard design characteristics including randomization and double-blinding reducing RCT costs dramatically and likely resulting in more rapid recruitment [18,19]. Opportunities exist for a variety of approaches to base RCTs within registries.

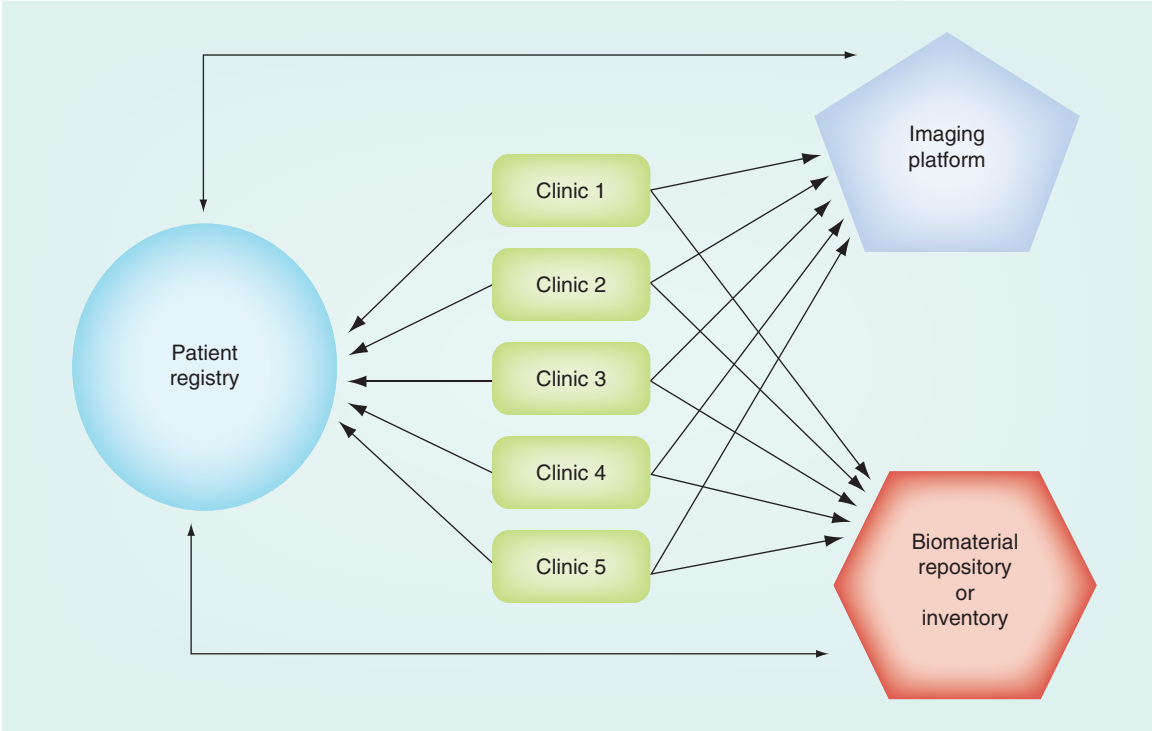

Figure 1. Interactions between primary patient registry infrastructure (clinic-based data collection) and linked data repositories.

Figure 2 demonstrates five designs for integrating an RCT within an existing registry. Figure 2A demonstrates direct recruitment from a registry into an RCT that is then run independently with no specific follow-up by RCT treatment allocation planned; Figure 2B demonstrates direct recruitment from a registry into an RCT, data management is provided by the registry and subsequent registry follow-up considers treatment allocation in the RCT. This allows for future data analysis possibly stratified upon new findings in the future (i.e., possible treatment responders and nonresponders based on new genetic breakthroughs). Figure 2C demonstrates direct recruitment from a registry into an RCT, data management is provided by the registry with subsequent registry follow-up but not considering treatment allocation in the RCT; Figure 2D demonstrates an RCT directly recruiting from a registry but with an independent electronic data capture system. During study visits, RCT selected outcome measure data are coentered into the registry resulting in capacity to compare in-RCT data to pre- and post-RCT data; Figure 2E demonstrates the same design as Figure 2D, except subsequent registry follow-up considers treatment allocation in the RCT for allowing for future data as in Figure 2B.

The importance of prospective longitudinal follow-up by treatment allocation following the conclusion of clinical trials is obvious. Factors affecting the efficacy of a given therapy within an RCT may be insufficient to exclude nonresponders at the screening visit. Such factors introduce bias and may result in a false-positive or false-negative RCT result. Similarly, the duration of the RCT may be too short to detect the effect of the intervention on the primary outcome. As an example, Cairncross *et al.* initially reported the findings of an RCT comparing procarbazine, lomustine and vincristine (PCV) plus radiotherapy (RT) versus RT alone for treatment of anaplastic oligodendroglioma with a primary end point of overall survival [34]. The initial publication of the RCT upon its completion, with 3-year follow-up on most subjects, reported no difference in survival benefit when stratified for age, Karnofsky performance score and degree of histological anaplasia [39]. Subsequent long-term follow-up incorporating 1 p/19 q codeletions on chromosomal testing revealed a mean overall survival of 14.7 years in the PCV/RT group versus 7.3 years in the RT alone group. In the subgroup without the codeletions there was no difference in overall survival (means: 2.6 and 2.7 years, respectively) [40]. Despite the methodological limitations of such unplanned subgroup analyses, these findings represent important evidence that chemotherapy in addition to RT prolongs survival with anaplastic oligodendroglioma. This example illustrates the value of long-term follow-up of RCT subjects well beyond the limited timespan of the original trial, and

retrospective incorporation of new knowledge. Registries represent an efficient and robust methodology for providing prospective observational data for a variety of applications and for RCTs in particular.

Electronic healthcare & the future: registries to improve clinical care & patient outcomes

Clinic-based or practice-based registries can also have an important impact on clinical care effectiveness and patient outcomes, especially for chronic disease management. Registries can be used to support clinical care through the collection of relevant data fields at routine visits to track longitudinal outcomes. Electronic- or web-based registries can provide additional benefits to clinical practitioners including the ability to examine cohorts and patient outcomes within a practice. Furthermore, registries can be utilized as a tool to enhance clinical practice including point of care reminders, decision-making tools and ongoing patient engagement. Registries may also improve the clinical outcomes of

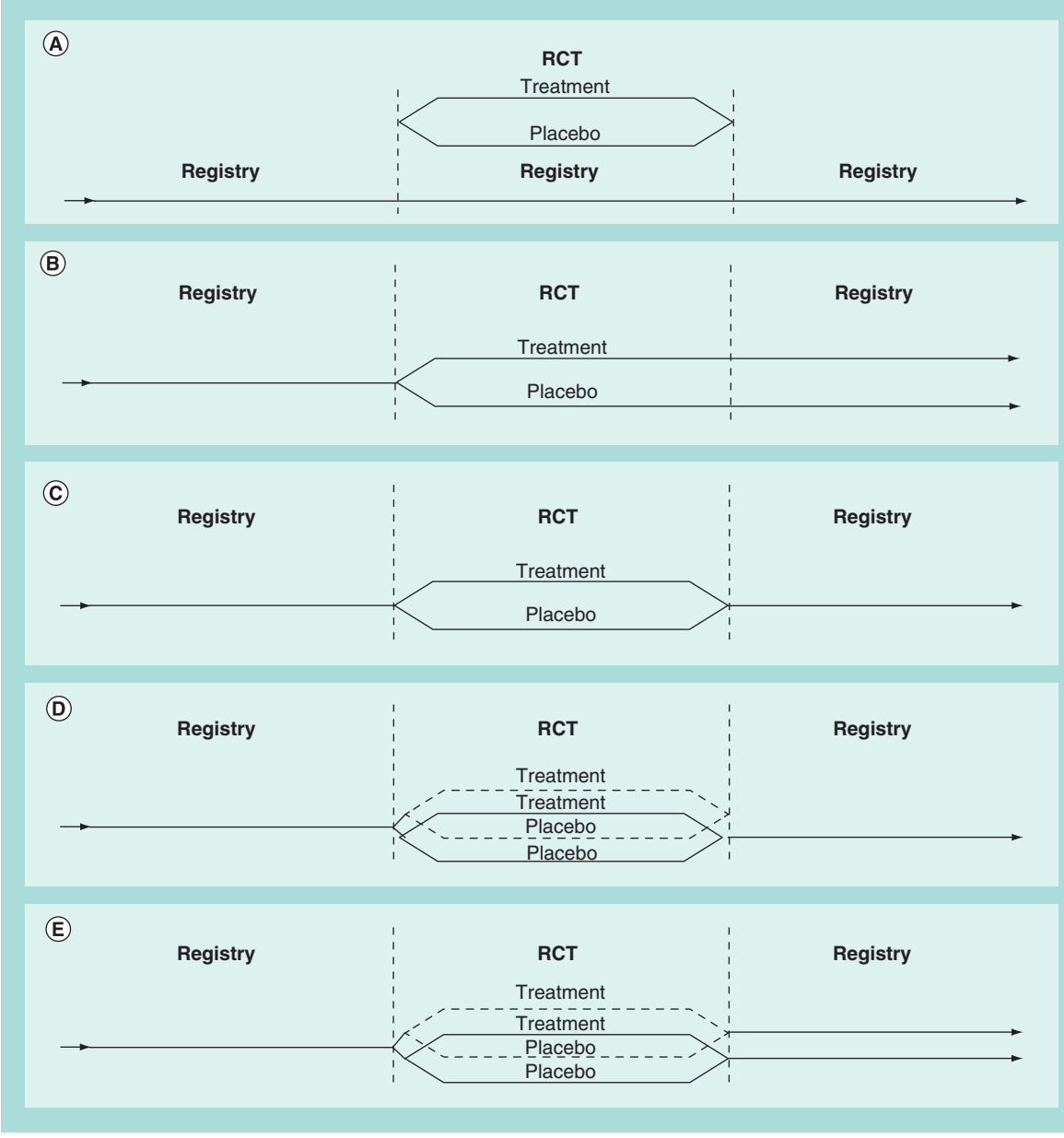

Figure 2. Possible designs for RCT integration within existing patient registry infrastructure. (A) Registry recruitment for separate RCT. **(B)** Registry-based RCT with perpetual registry follow-up by treatment allocation group. **(C)** Registry-based RCT without specific registry follow-up. **(D)** Registry-embedded RCT with double data entry into RCT EDC with no registry follow-up. **(E)** Registry-embedded RCT with double data entry into RCT EDC with registry follow-up.
EDC: Electronic data capture; RCT: Randomized controlled trial.

complex patients by providing reminders to physicians about individual treatment objectives allowing patients to be better engaged [41]. The nature of registries harmonizes well in the context of patient and clinician engagement with the concept of patient-accessible medical records (patient portals). These web-based systems typically allow patients to view their own medical records and may allow electronic communication with healthcare practitioners. They may also feature appointment scheduling, and patient education materials. Patients with rare neurological disease stand to benefit greatly from patient portals that provide complete and reliable educational material available on their disease to reduce the confusion generated by the results of a basic internet search. Further, if this information is available in the same portal to their clinicians, it simplifies the physician–patient interaction around material content. Contrary to popular beliefs, patient portals may be more enthusiastically used by lower socioeconomic groups than expected and improved access to information through patient portals may improve overall care outcomes within these underserved groups [42]. Sustained patient portal use can reduce patient stress associated with medical conditions [42] and in neurological care, this has the potential to impact patient- and family-perceived quality of life. To achieve maximum impact, neurological registries should combine patient-accessible and clinician-accessible medical records to improve patient outcomes and clinical research opportunities.

Conclusion & future perspective

Future neurological patient registries, especially those for rare disease groups, must consider the importance of robust methodology in their construction. Registries employing robust methodology and clear best practice concepts (e.g., multimodal recruitment and well-defined data elements) provide clear opportunities for innovative clinical research in areas not well served by traditional RCTs. These best practice registries in turn improve financial viability of clinical research and RCTs and provide data warehousing options and long-term follow-up opportunities previously unavailable within the relevant disease groups. Patient care outcomes in neurological disease may be enhanced by the creation of patient portals alongside registries to improve clinician–patient engagement and availability of reliable educational material. Neurological registries represent critical infrastructure needed to advance translational research in the long term, provide additional effectiveness depth to RCT findings and enhance the delivery of effective and efficient physician care.

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Practice points

- Neurological patient registries are an important platform for cataloging patient information for clinical research, administrative and regulatory purposes.
- The importance of standardization of data collected by registries is increasingly recognized due to the higher demand for larger patient cohorts and expanding opportunities for data linkage and sharing.
- Registry data can be linked to a broad scope of data modalities (i.e., neuroimaging, genetic and tissue bank data) enabling rapid and large-scale innovative data analysis.
- Randomized controlled trials can be operated upon existing registry infrastructure with low incremental cost and potentially with increased efficiency.
- Collaboration with patients through sharing of educational materials and patient medical information through registry patient portals will potentially enhance collaboration and improve participation in clinical research.

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