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Review

Innovative Interventional and Imaging Registries: Precision Medicine in Cerebrovascular Disorders

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Key Words

Registry · Imaging · Precision medicine · Endovascular therapy · Stroke · Atherosclerosis

Abstract

Background: Precision medicine in cerebrovascular disorders may be greatly advanced by the use of innovative interventional and imaging-intensive registries. Registries have remained subsidiary to randomized controlled trials, yet vast opportunities exist to leverage big data in stroke. **Summary:** This overview builds upon the rationale for innovative, imaging-intensive interventional registries as a pivotal step in realizing precision medicine for several cerebrovascular disorders. Such enhanced registries may serve as a model for expansion of our translational research pipeline to fully leverage the role of phase IV investigations. The scope and role of registries in precision medicine are considered, followed by a review on the history of stroke and interventional registries, data considerations, critiques or barriers to such initiatives, and the potential modernization of registry methods into efficient, searchable, imaging-intensive resources that simultaneously offer clinical, research and educational added value.

Key Messages: Recent advances in technology, informatics and endovascular stroke therapies converge to provide an exceptional opportunity for registries to catapult further progress. There is now a tremendous opportunity to deploy registries in acute stroke, intracranial atherosclerotic disease and carotid disease where other clinical trials leave questions unanswered. Unlike prior registries, imaging-intensive and modernized methods may leverage current technological capabilities around the world to efficiently address key objectives and provide added clinical, research and educational value.

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Introduction

Precision medicine has recently captivated the attention of biomedical researchers and clinicians across a diverse range of medical disciplines [1]. Emanating from the vast informatics potential unleashed by the Human Genome Project, the promise of genomic data has suggested that big data of various types may be used to inform personalized medical decision-making [2]. Such approaches may be of particular value in chronic and complex disorders, where many data may be leveraged to delineate the longitudinal or temporal course of a particular individual's health status. In cerebrovascular disorders, various types of data including neuroimaging may be used to discern telling patterns of complex neurovascular pathophysiology during acute stroke and into chronic phases of many conditions. The clinical implications of various therapeutic interventions, including endovascular therapy, are increasingly evaluated based on measures of long-term impact. Systems biology methodology or the -omics of cerebrovascular disorders that consider the interactions of numerous factors are contingent on such systematic collection, archival and analyses of big data. Although the predominant emphasis of precision medicine has centered on genomic data or novel exploration of the exome, imaging data offer similar potential and are already routinely acquired in most cerebrovascular disorders, unlike blood markers [3]. Imaging of cerebrovascular disorders will undoubtedly form a key element of future initiatives of precision medicine in stroke. Innovative imaging-intensive registries of interventional therapies provide an ideal platform to jumpstart precision medicine of cerebrovascular disorders, from acute stroke to more chronic management of intracranial and extracranial atherosclerotic disease, hemorrhagic diatheses and venous disorders.

Registries or phase IV trials constitute an essential element of translational research, yet such studies have historically been relegated to a subsidiary role in cerebrovascular disorders. This phenomenon may be attributed to the relative paucity of successful phase III clinical trials in stroke, resulting in the perceived reduced need for phase IV studies, commonly utilized for postmarketing surveillance. There has also been a chronic debate regarding the value of registries versus randomized controlled trials (RCTs) despite the fact that these studies serve distinct purposes. The availability of endovascular therapy in routine clinical practice for many years has resulted in a paradoxical and overwhelming mismatch between the volumes of cases treated in routine clinical practice versus the number of subjects enrolled in clinical trials [4]. Furthermore, the complex nature of various neurovascular lesions such as arteriovenous malformations or specific types of aneurysms has conjured the consideration of these pathologies as orphan disorders that remain unaddressed by large clinical trials. Nevertheless, these cases have likely generated vast amounts of clinical, imaging and angiographic data that have resided solely in disjointed medical records rather than registries.

The recent advances in technology, informatics and endovascular stroke therapies now converge to provide an exceptional opportunity for registries to catapult further progress in the understanding and definitive management of individuals with cerebrovascular disorders. There have been prior attempts to promote registries in stroke and interventional therapy, although imaging and angiography data have been superficially considered, largely relying on the inclusion of select variables or meta-data from individual readings rather than incorporation of actual imaging datasets [5]. As in phase III clinical trials, there has been a marked effort to reduce the burden or workload entailed with systematic collection of data, and the technology has only recently advanced to permit large-scale implementation of such a grand vision. Innovative approaches to incorporate routine imaging and angiography are now possible, forging an approach that will likely be augmented by proteomic, genomic and other -omic data in the future. Why now? At least five successful

RCTs of endovascular thrombectomy have recently transformed the landscape of acute ischemic stroke [6–10]. These influential trials established endovascular therapy and reperfusion of ischemic stroke based on the inclusion of imaging for selection of optimal candidates, incorporation of procedural metrics during angiography and the investigation of tissue impact on serial CT or MRI during the subacute period. Although divergent multimodal CT or MRI selection paradigms were used across these trials, all successful trials utilized some form of imaging to identify a favorable collateral profile [11–14]. Such potential imaging biomarkers, including the status of collateral circulation, have also been investigated in prior interventional studies of atherosclerotic disease [15]. In fact, the routine collection of noninvasive imaging prior to intervention and the automatic acquisition of angiography during such procedures markedly promotes the use of imaging to unravel the often-complex course of individual patients. In acute ischemic stroke, the role of phase III trials may shift to focus on evaluation of novel device technology or expanded indications or clinical applications such as an extended time window. Phase IV stroke trials or registries already underway are important to address broader generalizability and specific clinical impact of now established endovascular thrombectomy approaches. The restrictive and focused selection criteria of RCTs, such as the exclusion of M2 middle cerebral artery occlusions in recent thrombectomy trials, automatically generate further questions, whereas registries reflecting actual clinical practice may better answer these remaining quandaries [16]. It is unrealistic to expect there to be adequate resources and interest to develop an entirely new RCT for every subsidiary question that arises. Recent RCTs have spawned questions regarding low National Institutes of Health Stroke Scale (NIHSS) scores, low Alberta Stroke Program Early CT Score (ASPECTS), pediatric populations, distal occlusion sites and the role of advanced imaging. Even if adequate resources, interest and feasibility of RCTs are pivoting around these factors, it must be recognized that many of these factors are interrelated and dependent variables. For instance, patients with low NIHSS scores generally have higher ASPECTS and more favorable collateral profiles on advanced imaging. Rather than the reductionist approach of multivariable logistic regression analyses in RCTs that identify the most influential variables, alternative methods such as principal component analyses that consider interactions and the underlying systems biology of numerous variables in registries may be more informative. For intracranial atherosclerotic disease (ICAD), the lack of novel treatments after WASID, SAMMPRIS and VISSIT in past trials leaves many questions unanswered in the daily encounter with such patients [17–19]. For extracranial carotid atherosclerosis or stenotic disease, registries have been instrumental in advancing device technology for carotid angioplasty and stenting (CAS), whereas patient-specific factors such as symptom status await further clarification in the CREST-2 phase III trials of CAS and carotid endarterectomy [20]. Numerous questions therefore remain where registries and innovative approaches to big data may answer key aspects of cerebrovascular disease management.

The following overview builds upon the rationale for innovative, imaging-intensive interventional registries as a pivotal step in realizing precision medicine for several cerebrovascular disorders. It is understood that many other subtypes of neurovascular disease may not be addressed by such initiatives, yet such enhanced registries may serve as a model for expansion of our translational research pipeline to fully leverage the role of phase IV investigations. The scope and role of registries in precision medicine are considered below, followed by a review on the history of stroke and interventional registries, data considerations, critiques or barriers to such initiatives, and the potential modernization of registry methods into efficient, searchable, imaging-intensive resources that simultaneously offer clinical, research and educational added value.

Registries in Precision Medicine

Registries are optimal vehicles for implementation of precision medicine. The personalized or tailored nature of precision medicine to provide insight into the management of an individual patient is often alluded to as practicing medicine with an ‘n of 1’ [21]. Such an approach, however, is predicated on the availability of data to discern critical variables that reflect underlying pathophysiology and likely response to certain therapies. In routine clinical practice, most stroke care providers usually parse such data and make medical decisions case by case without definitive knowledge of how select variables are pertinent in a given case. Most commonly, care providers resort to population-based studies to yield evidence that may inform management of an individual patient, yet there is a wide gap between population-based analyses and determinants at the n of 1 level. The extent and depth of data collection in a registry determines the utility of such a resource to inform individual management of a patient. More extensive and detailed registry datasets have the ability to capture specific factors and patterns of variables that may be most informative. For instance, basic demographic variables such as age or sex may focus attention to a particular population subset, while adding increasingly specific dimensions such as baseline laboratory values or imaging findings may greatly enhance the value of such data to determine subsequent medical events. Most recently, the addition of genomics and sequencing of an individual’s exome holds promise to further refine such predictions [22]. This strategy is based on the assumed relevance of genomic information, comprehensive approach to assay the entire exome, exploration of systems interactions or higher levels patterns of variables and context where such analyses have been performed in other individuals beyond an n of 1. This systems-oriented, exhaustive approach to broad datasets is in radical contrast to traditional evidence-based strategies that strongly rely on RCTs previously reported.

Evidence-based medicine is strongly based on the foundation of observational studies and RCTs that focus on specific therapeutic interventions, yet registry data may address both patient-specific factors and a broad range of treatment variables. The limitations of RCTs are widely recognized; however, establishing new treatments for cerebrovascular disorders and stroke has been delayed at this stage of clinical research for many years, until recently. The intense focus on developing novel treatments in RCTs has inadvertently removed attention from patient-specific variables that are likely incredibly important in swaying the outcome of these subjects. The repeated failures or limited results of past stroke trials yielded a tremendous opportunity for investigation of subgroup analyses that often focused on patient-specific factors, fueling positive insight or pilot data for subsequent trials. Paradoxically, the recent positive endovascular therapy trials in acute ischemic stroke may be limited in their capacity to identify particular subset analyses of import, as most of these trials demonstrated the relative benefit of endovascular therapy in clinical outcomes across various subgroups. Analyses of RCTs, however, have largely endorsed a reductionist approach where only the most predictive variables are sought without considering the simultaneous broad array of variables or patterns that may be key. This is also driven in part by issues related to data collection in RCTs as discussed below that emphasize minimal cost and resource utilization during planning stages. There are also many clinical scenarios or constellations of treatments that can or never will be studied in RCTs for practical reasons. In stroke, complex interventions such as prehospital care, imaging selection, combined treatments, stroke unit care and rehabilitation efforts for the pathophysiology of a disorder as complex as cerebral ischemia may be very difficult to study in RCTs. Registries, however, do have this capacity depending on the scope and data specifications. In routine stroke care, registries such as GWTG and INSTOR have endorsed the fact that certain variables, outcomes and quality measures are generally informative and therefore should be systematically collected and even reported [5,

23]. Such initiatives are very important as the data would otherwise go uncollected and be remiss.

The sponsor and purpose of a given registry largely drive the scope and potential impact, yet considerable overlap may exist between such studies. Registries may capture important data on quality improvement efforts in routine clinical care, focus on specific treatments, study orphan diseases, spur pilot analyses, credential operators based on a threshold in expertise or case volume level, introduce iterations of device technology, assess generalizability of RCT results, measure radiation or contrast dosing and toxicity, survey certain ethnic groups or solely address the interests of a specific society or academic collaboration. Such practical distinctions will likely influence the nature of data considerations and ultimate added value, both discussed below. Common data variables pertinent to stroke care have already been recognized and endorsed as the NIH Common Data Elements (CDE) stroke-specific module, offering shared verbiage or language to describe these factors across registries [24]. Overlap clearly exists between registries established for different purposes, yet the sponsor or purpose of a given registry often limits the spectrum of data elements to the most critical variables in order to reduce effort, cost and ensure veracity of the resultant dataset. For example, an interventional registry may contain exquisite details on procedural details such as the time interval to delivery of a therapeutic device on clot interface, whereas other variables may be deemed less important. Quality improvement registries such as GWTG must balance the mandatory implementation of specific measures with the expected workload of acquiring and collating such data. Aneurysm studies or investigations of specific subtypes may leverage registry formats to acquire detailed measures such as computational fluid dynamic estimates of shear stress in a relatively smaller sample size or population. Pilot studies or lead-in phases to larger clinical trials may utilize registries as a means of credentialing the interventional expertise of specific operators and procedural measures, as with the Wingspan Registry for ICAD or the CREST-2 Registry for asymptomatic carotid disease [25]. As RCTs have known limitations, extrapolation to other clinical scenarios may require registries to assess generalizability as in the role of endovascular therapy for more distal arterial occlusions beyond the proximal middle cerebral artery segments [26]. Regulatory studies of contrast or radiation use in diagnostic imaging tests may focus on select aspects while not collecting data on other clinical elements. Finally, registries may be instrumental in studying the same disease or therapeutic intervention in a different ethnic or socioeconomic group. For instance, the relative predominance of ICAD in Asia may have different implications for acute endovascular stroke therapies due to the presence of intracranial plaque that may hinder device technology or, alternatively, more established collaterals that mitigate the response to therapy. Finally, groups of studies or trials and their primary results are often collected in registries such as clinicaltrials.gov.

Stroke and Interventional Registries

Registries have been implemented in a variety of cerebrovascular disorders and related interventional settings, although the variability in reporting standards and definitions has limited a comprehensive survey. As a result, stroke and interventional registries are extremely difficult to track down due to limited registration, and this is compounded by definitions of what constitutes a registry. Single-center series of stroke or interventional cases over a defined time period have been termed registries and regional or geographic collaborations have also been reported as registries. The nature of included variables has also varied, with definitions often unique to that particular study or series. In large, most stroke registries have not included neuroimaging to any degree. A few studies deemed registries have included

reports of imaging variables without methodology for centralized image archival or collection of actual imaging datasets [27]. This limitation removes the possibility of subsequent validation of results or re-interpretation by additional readers. This relative omission of imaging in stroke registries mirrors the saga of imaging in RCTs, where digital copies of imaging datasets are often not collected and local site interpretations are used without validation of such ratings. The lack of central imaging archival precludes further study of novel findings or post-processing methods. In stroke registries launched for quality improvement initiatives, some imaging metrics and even angiographic ratings such as the TICI score remain without validation or verification despite their use as quality measures for stroke care delivery or procedural performance [28]. Once again, the logistic aspects of imaging-intensive or detailed interventional registries have likely impeded such goals.

The potential of imaging-intensive and detailed interventional registries in cerebrovascular disorders is extensive. Interventional management of patients with cerebrovascular disorders has exceptional opportunities for data collection in registry format. Such patients are often followed over time, allowing characterization of the longitudinal impact of interventional therapies and to further understand the evolution of neurovascular pathophysiology. Even in acute ischemic stroke, evaluating the impact of emergency revascularization is primarily assessed by clinical outcomes at 3 months. Due to the considerable risk of recurrent stroke in many neurovascular disorders, such patients are often followed clinically and with serial imaging studies in tandem. Noninvasive imaging is often acquired, increasingly with angiography and perfusion imaging sequences, before and after conventional angiography acquired as part of the therapeutic intervention or in follow-up evaluation. In acute ischemic stroke, multicenter collaborative registries such as ENDOSTROKE have provided valuable data about endovascular therapy, including an extensive list of data elements, centralized and blinded imaging review, across a large volume of cases collected within a narrow study period [29–31]. Similarly, the NASA registry provided influential data on balloon guide catheter use in endovascular therapy [32]. The TRACK, STRATIS and Trevo registries will undoubtedly provide much more data and, importantly, answers to critical questions regarding routine clinical practices that go unanswered even after several pivotal RCTs [33]. The inclusion of centralized imaging and angiography would markedly enhance these registries. In past studies, such as the Merci Registry, such imaging methodology was unfortunately abandoned, and many questions remain unanswered, limiting the long-term impact of such an enormous investment [34]. Even when registries are restricted to data readily available from the medical record, there is the potential to inform subsequent studies. For instance, the routine noninvasive imaging acquired in parallel with the SAMMPRIS trial of intracranial angioplasty and stenting for ICAD has yielded novel insight, suggesting that an imaging registry of ongoing interventional therapies for this disorder may be further enlightening and rationally fuel subsequent clinical trials. Imaging analyses of ICAD or extracranial carotid disease with respect to cognitive or neuropsychology assessments may also be informative as recurrent stroke may not be the optimal choice of endpoints in studies of these disorders. For instance, the imaging-cognitive associations of cerebral hypoperfusion in asymptomatic carotid disease in CREST-2 may provide further dimension regarding the clinical impact of this disorder. Serial measures of such parameters may expand our current understanding of both ICAD and extracranial carotid disease. Complex aspects of endovascular care paradigms for these acute-on-chronic disorders such as timing of intervention or definitions for failure of best medical therapy may be addressed by dedicated imaging-intensive interventional registries where silent strokes and other sequelae may be monitored and piloted as novel biomarkers. In sum, numerous registry opportunities should not be forsaken, now that the logistics of imaging and other data elements are feasible.

Big Data Considerations

The era of big data has multiple potential dimensions in stroke, inferring extensive case volumes, unmatched depth with respect to the types of data elements and high impact on routine stroke care. The organization or schema of data collection is paramount. Most data from clinical trials or registries use relational database formats linked through unique subject or case identification numbers. These links are vital to ensure the integrity of the overall database structure yet this may not be the most efficient method for archival and continual updates while maintaining the ability to rapidly index, search and retrieve specific query results. As big data evolve, including massive datasets with actual imaging files may require novel formats for integrating complex datasets composed of source imaging files with the abstracted imaging variables, clinical and other parameters such as laboratory or genomic data. The nature of data, whether in stacks of imaging files or in the format of genomic or proteomic profiles, will need to be incorporated rather than used according to the established concept of one spreadsheet cell for each variable code or value.

A dynamic dataset model will be imperative, in contrast to the current use of master datasets that are locked and immutable once all final data elements are verified. In most clinical studies, a final version of the trial or registry dataset is verified, cleaned and locked to all future users for preservation of a master file. Each subsequent clinical study essentially starts from scratch to begin accumulating data against a blank slate. Dynamic datasets that allow continual updates to the master file, including either additional variables or values at later time points, will be essential. A snowball metaphor or model of data accumulation with the application of successive layers and incremental momentum is most apt to describe this approach. Even when all data elements of a clinical study are ‘finalized’ with respect to an individual subject, subsequent health events may be important to track, additional readers of imaging studies may add their own interpretations, more parameters may be generated from novel postprocessing methods or newly recognized imaging signs and proteomic or genomic assays may be added from stored blood samples. The prevailing emphasis on temporal changes in health status and long-term clinical outcomes underscores the need to incorporate later events that may not occur within a defined study period. The episodic nature of acute stroke and interventional treatment has reinforced the notion that registry entries should include enrolment of subjects only at the time of each qualifying event, rather than focusing on all the cerebrovascular events occurring in a given individual once identified. For example, both GWTC and INSTOR capture recurrent strokes in a given patient based on each episode that occurs rather than tying these important data elements together. Recurrent treatment or intervention for subsequent cerebrovascular events may be difficult to track in current systems unless the events occur within an expected time frame. For instance, tracking repeated transient ischemic attacks in a patient with ICAD or the progressive cognitive changes in certain disorders may be difficult to track unless an arbitrary study time window or period is implemented. Finally, such a dynamic data model mirrors the acceleration in biomedical technology that may continue to shed light on population studies collected in this manner, rather than lock and store such datasets in a relatively archaic fashion.

The potentially daunting task of defining the key or most relevant variables in a registry that evolves over time has been simplified by the establishment of the CDE [24]. A broad range of CDE has been exquisitely defined for stroke, including standard definitions and example case report forms. As new measures such as key time intervals between procedural steps of interventional therapy are endorsed, these variables may be added to the dynamic dataset. The inclusion of centralized imaging and angiography data allows for the potential verification of intervals such as the time to earliest reperfusion, even when such data are not captured in the initial data abstraction. A plethora of imaging variables may also be included

in future data analyses, yet it may be sufficient to utilize only the minimal imaging CDE if the source image files are archived at a central core laboratory.

This dynamic model of data architecture for an innovative registry also emphasizes a central tenet that data are meant to be used, rather than just stored. Storing data in a repository is inefficient, and even pointless, unless they are actively used for future analyses. In clinical registries, the incremental addition of each case is most informative when the new case is contrasted with prior benchmarks or past data in the registry. For instance, real-time feedback on time metrics for the delivery of stroke care is a potent strategy to continually enhance patient workflow and eliminate delays. Such continued refinement or iterative methods may be similarly applied to interventional techniques. For imaging data, the uploading or initial stage of building a repository is quite literally only the first step. The imaging data are a valuable resource that should be repeatedly tapped rather than removing any linkage with the remainder of the clinical datasets, as has happened with past stroke trials and registries.

The iterative addition of further data layers in this dynamic or snowball dataset model allows for quite complex arrays of data to be analyzed at each subsequent stage, leveraging the advanced computational methods of precision medicine. The systems biology and complex interactions may be studied with this approach rather than resorting to the reductionist model of finding only the most potent isolated variable. For instance, the therapeutic response to endovascular therapy and even the time-sensitive nature of specific interventions may be discerned once collateral status is added to the model. As further variables are added to such a complex dataset, precision is refined and the course of an individual patient may be better ascertained. Questions remain regarding the required level of precision for routine medical decision-making, yet data registries can only enhance this process. Systematic data collection is now part of various standard quality improvement initiatives for comprehensive stroke center certification. These routine clinical metrics are valuable as pooling similar data from a variety of RCTs is fraught with difficulties due to the individual assumptions and selection biases of each trial. For instance, detailed consideration of numerous variables is necessary to unravel the curious finding of incredibly low hemorrhagic transformation rates in recent trials. There is likely a need to combine numerous factors such as baseline imaging selection, treatment and timing, to explain hemorrhagic transformation and, perhaps most importantly, validate the interaction of such parameters in a registry format.

Critiques or Barriers to Registries

The implicit debate regarding the relative role of registries versus RCTs has fueled criticism that has impeded the establishment and growth of registries. As noted above, registries serve a distinct role compared with RCTs, complementing earlier translational research phases and providing an important juncture with patient care across diverse clinical settings. Research agendas and scarcity of funding opportunities may drive this debate, promoting RCTs and the resulting evidence as priority over registry studies. Registries, however, serve broad purposes and are used extensively in cancer, infectious disease, trauma and cardiovascular disorders where outcomes research and public health impacts are greatest. Similar potential of registries in cerebrovascular disorders and interventional therapies is indisputable. Potential barriers to registry implementation mirror RCT considerations, including accuracy of data, security or privacy concerns, workload, cost and ultimate need. Such critiques and scrutiny remain an issue in the design and conduct of RCTs but may be similarly addressed within the context of registries. In fact, the platforms and data infrastructure of RCTs may be used for associated registries. Registries may run in parallel with ongoing RCTs, providing important contempo-

aneous data to complement the trial primary results as in REVASCAT and the associated SONIA Registry [7, 35]. This may be important, as many recent RCTs may not keep screening logs to reflect those cases that were not enrolled. Potential RCTs of endovascular thrombectomy for patients with low NIHSS scores or, conversely, low ASPECTS would be useless without detailed knowledge of all the patients excluded from such trials. Such parallel RCT and registry enrolment has been discouraged due to fears of detracting from recruitment goals of the RCT, yet registries can answer many more and broader questions about generalizability than an RCT. There has been concern that registry data may not be as rigorously culled or verified due to the perceived subsidiary role with respect to RCTs and closely regulated investigations. Perhaps the greatest incentive to ensure data veracity is through academic interests of participating investigators that strive to achieve meaningful scientific collaborations and feedback about the relative impact of their own data. Rather than being cast as haphazard in organization, phase IV registries may use the same oversight via regulatory bodies to carefully monitor data integrity. Until recent stroke and interventional trials achieved positive results, there may have been limited sponsor or industry interest in registries. Device manufacturers will undoubtedly be interested in supporting registries that may expand therapeutic indications ultimately approved by regulatory bodies. The academic competition between sites to enroll the maximal number of patients in an RCT may also be leveraged in a registry. High enrollers may gain publication opportunities and other leading roles. Concerns regarding fabricated or inaccurate data entry may be checked by verification of annual case volumes through Medicare payment by diagnosis-related group data provided by the Center for Medicare and Medicaid Services. Furthermore, the inclusion of imaging and angiography source data in a registry allows for central review or verification of data integrity and quality control. Security concerns regarding dissemination of data and privacy relating to HIPAA legislation may be readily addressed through systematic de-identification. Distribution of de-identified public registry datasets would adhere to the same policies expected of RCTs for secure data sharing. The workload or burden of contributing to a registry largely hinges on the time-consuming abstraction of certain variables from the medical record or interpretation of specific raw data. If the local site is asked to send mostly primary or raw data, then such efforts may be reduced. From the patient perspective, informed consent can be included at the time of hospital admission, covering the inclusion of all data acquired during hospitalization. Furthermore, the CDE definitions have clarified and standardized data descriptions. The implications of missing data are not as profound as in RCTs, and the strict adherence to protocols and potential deviations are actually less of a concern in registries where the goal is to ascertain variability in routine clinical practice. Despite efforts to minimize the workload of registry participation, such initiatives cannot be mandated unless by government decree. Conversely, sites should not be selling their data but contributing to scientific collaborations. Blinding is not typically necessary for registries, unlike RCTs. In addition, the scientific goals of a registry are far wider than the hypothesis-driven framework of an RCT. It has been argued that rational data collection should always be centered around clearly delineated hypotheses, yet this may not be accurate as registry data may be used to generate, rather than prove hypotheses. Standardizing or utilizing the same technology may be a concern in RCTs, yet registries over prolonged periods may actually incorporate novel methods such as imaging techniques that continue to evolve.

Modernization of Registry Methods

The implementation of innovative interventional and imaging registries may leverage recent advances in technology. As mentioned above, efficient data architecture and active flow of data from local sites to central core with rapid feedback are necessary. The inflow of

data may now leverage web-based portals that can securely transmit all types of information, including standard clinical case report forms and entire imaging and angiography datasets. Real-time data entry can synchronize registry progress with the busy pace of routine clinical care. Minimizing additional workload for the local investigators or coordinators is essential, and this may be achieved by using primary data such as lab values that can be exported from another dataset or by capturing all neuroimaging or angiography studies and series acquired during hospitalization for an index event. It is imperative to avoid extra steps in manual entry or selective data interpretation or abstraction. The transmittal of the imaging and angiography datasets allows for verification of other clinical data or reported procedural variables. This important quality control step should therefore be conducted by the central core lab at the time of closely synchronized image review with respect to registry enrolment and not merely as a function of image upload. For example, time to reperfusion in acute stroke or degree of stenosis in atherosclerotic disease may be centrally adjudicated directly based on imaging with respect to local reported measures. Imaging-intensive registries thereby provide internal validity.

The infrastructure of such innovative registries may deploy a wide base of investigators across the globe while coordinating core laboratory administration via centrally organized expert panels. Such an inclusive model invites participation based on local interest in data and leverages the collaborative expertise of distributed, yet experienced, imaging readers. Imaging core lab experts may routinely abstract the basic stroke imaging CDE to allow for standard comparisons and replication, while additional elements of the hierarchical CDE can be added later. If feedback is generated to the local site regarding their data and comparisons with larger cohorts, this incentive may drive further registry expansion akin to crowdsourcing models. Technical requirements include massive data storage beyond petabytes, rapid processing and high-speed data transmission. The snowball model of a progressively expanding relational database can simultaneously allow indexing to be easily searchable while adding incremental layers of postprocessed imaging, additional data elements or innumerable readings of particular imaging or angiographic findings by various readers. The digital format of clinical and imaging data can also be supplemented by later integration of genomic arrays. Such structure allows for large-scale investigation and subset analyses on specific cerebrovascular disorders, subtypes or particular therapeutic strategies.

Added Value of Innovative Registries

The efficient organization and dynamic use of big data in cerebrovascular disorders may enable precision medicine in stroke by integrating the abundance of information on key pathophysiology embedded within routinely acquired imaging and interventional datasets from around the world on a daily basis. The numerous questions resulting from recent RCTs of endovascular thrombectomy in acute stroke, pilot data on ICAD for future trials and the impact of available carotid revascularization approaches may be gleaned from innovative registries and directly linked with long-term patient outcomes. The added value of such an approach stems from the simultaneous focus on academic or research questions, progressive refinement or quality improvement of routine clinical care and the resulting educational opportunities. The local investigator may be motivated by interest in critically evaluating their own data or inspired by global comparisons, intrigued by different perspectives on image interpretation and enticed by authorship or other academic opportunities. Such collaborations across centers and borders are now possible due to information technology systems that enable rapid data transmission. After enrollment of each subject in a registry, immediate

feedback to a local site with their performance regarding selected treatment measures may continually improve stroke systems of care in diverse clinical settings. When combined with the associated clinical outcome data, such report cards may highlight novel opportunities to improve clinical management. Existing data sharing plans for clinical and genomic data may now be augmented with similar protocols for imaging data. The interaction and comparison between local and centrally adjudicated imaging features or angiographic aspects of interventional procedures provide an educational forum to teach and train an increasing pool of potential future central imaging experts. There is no limit to the number of potential imaging observations that may be added to a registry teaching resource. Economies of scale increase the relative productivity of a central imaging and angiography core lab with demonstrated expertise in past stroke clinical trials. The sample sizes or case volumes of such registries may dwarf the size of equivalent RCTs, allowing for conclusions that are more potent regarding specific variables. Furthermore, the less restrictive selection criteria of a clinical registry introduce greater heterogeneity and more opportunities to explore practical aspects that arise in routine clinical care. Even once the relationships between certain variables are recognized, such as the link between time from symptom onset in acute stroke, NIHSS score, ASPECTS and collateral grade, it may not be possible to conduct an RCT around these inter-related factors. Many treatment questions may go unanswered in RCTs yet explicated in registries, such as the role of head positioning in acute stroke, the impact of adjunctive treatments or specific rehabilitation interventions. Perhaps most important is the unique opportunity to investigate serial or longitudinal data regarding both the imaging and clinical course of an individual with cerebrovascular disease. Detailed analyses of such extensive datasets are possible with systems engineering, machine learning and other advanced computational methods of precision medicine as recently endorsed by the National Institutes of Health and major academic institutions.

Conclusions

Innovative models of registries that embrace recent technological advances to incorporate the serial imaging and angiography of interventional management in a variety of cerebrovascular disorders may enable precision medicine in stroke and other cerebrovascular disorders. There is now a tremendous opportunity to deploy registries in acute stroke, ICAD and carotid disease where other clinical trials leave questions unanswered. Unlike prior registries, imaging-intensive and modernized methods may leverage current technological capabilities around the world to efficiently address key objectives and provide added clinical, research and educational value.

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