Research methodology and practical issues relating to the conduct of a medical device registry

Theodosios Bisdas1,2, Patrick Bohan3, Mario Lescan4, Clark J Zeebregts5, Jörg Tessarek6, Joost van Herwaarden7, Jos C van den Berg8, Carlo Setacci9 and Vincent Riambau10

Abstract

Background: The postmarket research goal is to assess “generalizability” or “external validity” to see if the early results of clinical trials with investigational devices are reproducible in everyday practice in the real world and the longer term. Registries have an important but ambivalent role in achieving this goal.

Methods: Although registries are common, in practice they follow the regulatory processes that appear designed primarily for pharmaceutical clinical trials and confirmatory studies. We review the literature to assess different definitions and the role of registries in the hierarchy of scientific evidence. We analyze common characteristics affecting registry design, implementation, and governance as well as safety reporting and off-label use while describing the experience of setting up an international, prospective registry for an endovascular device used to treat abdominal aortic aneurysms.

Results: Key areas in which to distinguish registries from trials are as follows: eligibility, setting (patients and institutions), device configurations and iterations, the use of design and quality “spaces,” a focus on systematic quality checks (rather than source data monitoring), open-ended follow-up, flexibility in the definition of end points and sample sizes, data sharing, and publishing commitments.

Conclusion: Both clinical trials and registries are essential and complementary research methods and the strengths and weaknesses of each need to be recognized. The specific characteristics of registry research deserve to be acknowledged and safeguarded in the regulations governing clinical investigations with medical devices.

Keywords

Registry, device, methodology, endovascular, stent graft, pragmatic, non-interventional, observational, real-world evidence

Background

Postmarket surveillance is the process of continuing assessment of safety and effectiveness after a medical device is authorized for commercial use. The postmarket research goal is to assess “generalizability” or “external validity” to see if the early results of clinical trials with investigational devices are reproducible in everyday practice in the real world and the longer term. The European Union’s (EU) Medical Device Regulation 2017/745 requires a “systematic procedure to proactively collect and review experience gained from devices […] on the market […] for the purpose of identifying […] any necessary corrective or preventive actions.” This requirement has often been met with postmarket clinical follow-up studies referred to as registries (to distinguish them from trials with...
investigational devices and confirmatory studies), which are characterized by a large scale (both in number of participants and duration) and an observational nature.

Although registries have a long history (a leprosy registry in Norway dates from 1856) and are common (one calculation reported 1028 registries in the EU; 83 of which were device registries), they are less well known and understood than clinical research methodologies required prior to marketing approval and often sit awkwardly in a regulatory environment designed primarily for pharmaceutical clinical trials and confirmatory studies.4–6

The objective of this article is to describe the characteristics and uses of registry research, discuss some of its practical and ethical implications, and suggest ways to improve its organization and conduct.

**Methods**

**Definitions and terminology**

A registry assesses effectiveness of authorized products in standard clinical practice and, along with low-intervention clinical trials and postmarket research, is “pragmatic research.” In contrast, efficacy is assessed in the well-defined and controlled setting of clinical trials and “explanatory research.”7 The objectives of pragmatic research are as follows: (1) to inform decision-makers (patients, clinicians, administrators, and policy-makers) rather than exploring a biological or social mechanism, (2) to enroll patients representative of the populations and clinical settings, and (3) to streamline procedures and data collection (to focus on adequate power) or to measure a broad range of outcomes.8

Is a registry the appropriate tool for pragmatic research? Some definitions are too vague (“any system that collects uniform data”) to distinguish a registry from a trial.9 The many other definitions detailed in Table 1 demonstrate the great variety available and what consensus exists, but point to an essential problem that too much registry research is conducted in isolation.

The common elements of registries that stand out are observational, public health, and long-term objectives as well as high patient coverage (close to 100% of the patients with a target disease or treatment) and purposeful. Many clinical data are collected for a variety of practical reasons (e.g., administrative) and subsequently analyzed systematically.9,11 Other characteristics include a defined population and naturalistic (or “real world”) data collection in contrast to the carefully selected populations of clinical trials.13 The International Medical Device Regulators Forum’s definition prioritizes the aspirational objectives to increase knowledge and improve care (Appendix 1 of Supplemental Material).18,19 In an analysis of registries by Bouvy et al.,21 the following criteria defined registries: postauthorization, non-interventional, no inclusion criteria other than the use of the product (in case of a product registry) or a diagnosed condition (in case of a disease registry), and long-term follow-up (minimum 2 years).

**Registries and medical devices**

There are several factors specific to medical devices that make registries appropriate as a research methodology: uncertainty about long-term outcomes in what are often permanent implants, substantial design variation within a class, the potential for clinically significant variation in outcomes across populations, high cost, difficulty in blinding (randomization may be impossible or even unethical), confounding factors (such as operator experience and preference with regard to device sizing), patient and device selection, and continuous device changes and developments.22,23 It may be impossible to tease out the individual effects of the many different components and different settings, so a “package of care” needs to be assessed.24

An ideal registry will give a larger perspective (with national, regional, or global benchmarking) and allow prospective monitoring to pick out faulty device designs or procedures with higher than expected failure rates. The objectives of the American Joint Replacement Registry, for example, “are to define the epidemiology of total joint arthroplasty and to monitor its clinical outcomes.”25

Orthopedics has a long and successful history of national registries with the first being the Swedish Knee Registry set up in 1975 (which now includes 284,000 primary total hip arthroplasties from every hospital in the country) and between 13 and 24 currently active in hip/knee arthroplasties.6,26

Randomized controlled trials may be the gold standard in clinical research but they are not without limitations (such as monitoring of long-term outcomes) and may have a lower impact in terms of median citation counts.26–29 Furthermore, there are very specific problems involved in randomizing patients to surgical interventions that mean that most innovative surgical procedures were not tested in randomized controlled trials.30 This is not to say that registries are always better but to argue for the correct application of the most appropriate research methodology to bridge the gap between randomized trials that lack generalizability and observational studies that lack internal validity.31,32

The balance between the different methodologies is compromised because registries can be forced to adapt to pharmaceutical clinical trial requirements in the absence of registry-specific requirements.21,33 Whatever way we define registries, they should be comparable with low-intervention or non-interventional studies and so-called “large simple trials,” embedded in standard
Table 1. Registry definitions.

<table>
<thead>
<tr>
<th>Source</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellows10</td>
<td>A system of recording frequently used in the general field of public health [...] for the administration of programs concerned with the long-term care, follow-up, or observation of individual cases [...] recorded over a period of time.</td>
</tr>
<tr>
<td>World Health Organization11</td>
<td>A file of documents containing uniform information about individual persons, collected in a systematic and comprehensive way, in order to serve a predetermined purpose.</td>
</tr>
<tr>
<td>The Professional Society for Health Economics and Outcomes Research (ISPOR)12</td>
<td>A prospective observational study of subjects with certain shared characteristics, which collects ongoing and supporting data over time on well-defined outcomes of interest for analysis and reporting.</td>
</tr>
<tr>
<td>Agency for Healthcare Research and Quality (AHRQ)13</td>
<td>A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves one or more predetermined scientific, clinical, or policy purposes [...] in which the following are true: The data are collected in a naturalistic manner (the management of patients is determined by the caregiver and patient together and not by the registry protocol). The data collection is purpose driven rather than the purpose being data driven (limited to or derived from what is already available in an existing data set). The registry captures data elements with specific and consistent data definitions. The data are collected in a uniform manner for every patient (both types of data and the frequency of their collection). At least one element of registry data collection is active (some data are collected specifically for the purpose of the registry rather than inferred from sources that are collected for another purpose (administrative, billing, pharmacy databases, etc.).</td>
</tr>
<tr>
<td>European Medicines Agency (EMA)14</td>
<td>Organized systems that use observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time.</td>
</tr>
<tr>
<td>US Food &amp; Drug Administration (FDA)15</td>
<td>A system that collects and maintains structured records on a specific disease, condition, procedure, or medical product for a specific time period and population.</td>
</tr>
<tr>
<td>Clinical Trials Transformation Initiative (CTTI)16</td>
<td>An organized system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition, or exposure. At their core, registries are data collection tools created for the purpose of generating clinically usable information and evidence. Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug, device, or other treatments (exposure registry).</td>
</tr>
<tr>
<td>Cross-border Patient Registries Initiative (PARENT)17</td>
<td>An organized system that collects, analyses, and disseminates the data and information on a group of people defined by a particular disease, condition, exposure, or health-related service and that serves a predetermined scientific, clinical, and/or public health (policy) purposes.</td>
</tr>
<tr>
<td>International Medical Device Regulators Forum (IMDRF)18,19</td>
<td>Organized system with a primary aim to increase the knowledge on medical devices contributing to improve the quality of patient care that continuously collects relevant data, evaluates meaningful outcomes, and comprehensively covers the population defined by exposure to particular device(s) at a reasonably generalizable scale (e.g. international, national, regional, and health system).</td>
</tr>
<tr>
<td>International Organization for Standardization (ISO) 14155 standard (draft update)20</td>
<td>An organized system that uses observational methods to collect defined clinical data under normal conditions of use relating to one or more medical devices to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure and that serves predetermined scientific, clinical, or policy purposes.</td>
</tr>
</tbody>
</table>

care and requiring minimal additional effort from physicians and patients and fewer resources.34,35

Results

Based on the literature and anecdotal evidence, Table 2 describes characteristics associated with registries. When Tables 1 and 2 are compared, we can see practically how a registry might be distinguished at the methodological and regulatory levels from a clinical trial.

Eligibility, recruitment, and setting

Core to the nature of registries is how and where patients are included (or not included), not just eligibility and recruitment but also setting (which institutions will participate).36 A general objective is to achieve high (if not 100%) patient coverage, and, thus, an ideal registry will be embedded within clinical practice.9 Dramatically reducing eligibility criteria, removing barriers to accrual, and early consent have been identified as key ways to simplify research.37

Registries also need to be comprehensive to increase power and compensate for possibly poorer quality data. The quality of registries as described in a systematic review of 147 articles was poor with a median study score of 4 (range 3–8) using the Newcastle–Ottawa Scale (maximum score of nine).38 Part of the reason for this is that registries are more prone to biases, especially selection bias, than randomized trials, and
non-consecutive enrollment can introduce substantial systematic bias as excluded patients have worse outcomes.\textsuperscript{39,40} Selection bias means that the procedures used to select study subjects lead to an effect estimate among those participating in the study that is different from the estimate that is obtainable from the target population.\textsuperscript{39} Total coverage will avoid bias but informed consent is not compatible with unselected, consecutive enrollment.\textsuperscript{41–43} Patients who agree to participate in a registry may be qualitatively different from those who do not, and this difference can compromise external validity.

There might be an incentive to avoid enrolling patients at higher risk of complications both because of the additional work involved and how that might reflect on the researchers or their institutions.\textsuperscript{44,45} One suggestion is to randomize the selection of investigative sites as it is possible that centers that are more compliant with guidelines might be more likely to participate in research.\textsuperscript{46}

The traditional approach to data protection for research relies disproportionately on informed consent over alternatives such as data anonymization.\textsuperscript{47} Other possible solutions described in the literature are integrated (clinical and research) consent, targeted consent, and broadcast consent.\textsuperscript{48} Patient data can be collected in a registry either by the patient’s explicit consent or based on law. Large population-based patient registries in Scandinavia were established by law without patient consent.\textsuperscript{5} The UK Renal Registry can also collect data without individual patient consent under Section 251 of the National Health Service Act.\textsuperscript{*} The US Institute of Medicine suggested that informed consent for some research using electronic health records might not be required as obtaining permission from patients is too burdensome.\textsuperscript{49} A recent report asked whether a registry using data collected for non-research reasons (e.g. electronic patient information) constitutes research, whether registries can be exempted from consent requirements, and what registry data are considered protected health information.\textsuperscript{22} The EU clinical trial regulation allows for a simplified informed consent to be obtained in single-country, low-intervention cluster trials where groups rather than individuals are allocated to a treatment (Article 30 and Annex I.L.62).\textsuperscript{50}

Consent in registries, therefore, depends on the balance between respecting data privacy and their public


---

**Table 2.** Observed characteristics of a registry.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility</td>
<td>Inclusion in a registry is simplified to whether a patient received a treatment or not. Exclusion is minimized to make the data set as comprehensive as possible and avoid selection bias.</td>
</tr>
<tr>
<td>Recruitment</td>
<td>All possible and consecutive patients need to be enrolled so that size or power compensates for missing or mistaken data. A sample size calculation may not be necessary if the objective is to include all patients treated (over a certain time period or perhaps indefinitely).</td>
</tr>
<tr>
<td>Setting</td>
<td>Data are collected to reflect standard clinical practice (“real world data”) across a wide geographic area and a variety of institutions and over a long time. Real-world use includes off-label use.</td>
</tr>
<tr>
<td>Flexibility</td>
<td>It is not necessary (or possible) to standardize all elements of the intervention. Design variation in a class of products (e.g. the different sizes and configurations of stent grafts) or operator/institution variability will be captured by sufficiently large amounts of data.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>There may not be a primary outcome because the registry can be used for multiple purposes and a range of end points. The registry may facilitate subsequent trials and research and will have a purpose rather than a hypothesis; part of the attraction of a large data set is precisely to allow exploratory and post hoc analyses. Protection of personal data as well as improvements in quality can be served by adhering strictly to the principle of collecting the minimum amount of data necessary to meet a registry’s purpose.</td>
</tr>
<tr>
<td>Design</td>
<td>A registry is observational (non-interventional or low-intervention) in a specific population defined by a particular disease or treatment. A registry can be prospective or retrospective. A registry can be open-ended (continuous patient enrollment) or at least a fixed enrollment period with a very long follow-up period.</td>
</tr>
<tr>
<td>Governance</td>
<td>Registry holders are predominantly public or not-for-profit bodies. A registry has a public interest or policy objective. A registry requires fewer resources than clinical trials and should be easier to conduct.</td>
</tr>
</tbody>
</table>

---
policy role. One possible solution might be to make the device and not the patient the focus of the registry. The European Registry for Abdominal Wall Hernias, for example, registers hernia operations and not patients. Another ethical consideration is outside-instructions for use (IFU) deployment of devices (or off-label in the context of drugs). One study has reported up to 70% of the patients failing to meet labeled requirements while more generally reported around 20%. Should a registry be a tool for proactive, postauthorization risk assessment that is observational and non-restrictive (to include a diverse patient population perhaps not represented in early clinical trials) or must it restrict eligibility to the patient population defined in early trials? Ideally, one of the advantages of a registry might be to study the performance of an approved device for a new indication; “indication creep” is actually a stage in the IDEAL-D (Idea, Development, Exploration, Assessment, Long-term study) framework designed to improve the quality of research in surgery. The Transcatheter Valve Therapy registry, for example, showed that a transcatheter valve approved for femoral artery access was also safe and effective using a transapical approach. (The same registry was also used by the US Medicare system in its “Coverage with Evidence Development” program that reimbursed the device on the condition that outcomes data were captured.) There are, in fact, two different issues here: (1) when (if ever) is outside IFU justifiable and (2) when it does happen, clinical data need to capture both its extent and outcomes if we wish to address seriously the first question.

Outcomes and end points

Some registries were set up originally for clinical purposes (e.g. a contact database to facilitate notifications or share information on transplants) and only later developed a research function; thus, many have functioned for years outside the established research structures and requirements and without the typical study protocol elements of primary and secondary objectives and sample size calculations. It is now possible for pharmaceutical trials to be “embedded” or “nested” in registries; the registry contains only raw data from which a hypothesis is generated and can be “mined” by a trial protocol to confirm or disprove. A registry therefore may have no hypothesis but constitute only a data collection structure or a data source within which subsequent studies can be performed which answer a specific research question (i.e. confirmatory studies). This aligns with the International Medical Device Regulators Forum which defines registries in terms of the general need to “increase knowledge” implying that there may not be a specific hypothesis (Appendix 1 of Supplemental Material). How many patients are enough for a registry? The answer depends largely if there really is a primary end point (like a clinical trial and therefore needs adequate power) or whether it is open-ended and aims to measure a broad range of outcomes over a long period of time. A systematic review of 147 articles reporting on 27,058 endovascular repair patients recommended consensus end points of cumulative endoleak rate (excluding type II) and reintervention rate at 2 years and defined non-inferiority as better performance than the worst performing 25% of the stent grafts. To demonstrate an end point like stent graft non-inferiority after 2 years, the authors concluded that 525 endovascular repair patients are needed (only two registries they analyzed were adequately powered). In contrast, the US National Cardiovascular Data Registry does not have a primary end point but aims for “data collected once and used for many purposes.”

Design and governance

Can a registry be limited to a single device? Methodologically, yes, but can registries organized by manufacturers be compatible with the public health and policy aspects of registries? A survey identified only 3%–6% of the registry holders from industry (52% were a national government authority). The experience in orthopedics and the US national arthroplasty registry, for example, points to the need to involve all stakeholders (surgeons, learned societies, industry, and regulators), but an international and device-specific registry faces the disadvantages of not having total coverage (all interventions, unless there is only one device on the market) and the difficulty of facing different and sometimes contradictory public policy requirements.

Regulators have generally prioritized patient registries over product registries because they allow comparisons, facilitate risk stratification, and confounder adjustment; disease registries are also generally better integrated into health-care systems. This is a challenge for the aortic aneurysm field where manufacturers’ device-specific registries have been ongoing for some time, and disease registries (both endovascular and open surgery) or treatment registries (all endovascular repairs, not device specific) are limited (geographically or to specific questions) and data sharing is uncommon. Interestingly, a non-commercial registry such as Vasconet (a collaboration of national and regional registries from 10 countries) is long established in the field of open aortic repair as is the European Registry of Endovascular Aortic Repair Complications in thoracic endovascular repair. The Society for Vascular Surgery endovascular repair reporting standards should serve to collect uniform data across sites and countries in the same way as the Cardiology Audit and Registration Data Standards do for cardiac registries.
The American Joint Replacement Registry and the International Society of Arthroplasty Registers are collaborating with the medical device industry to link data from international registries and establish global standards for device surveillance and postmarket research.25

Will size make up for the probable deficiencies in terms of confounding factors, missing data, and so on?46 Large patient numbers may be more important in providing credible results than close monitoring of data points.69 There may be an acceptable level of error for certain data types, and the intensity of monitoring can vary accordingly. If an error does not affect the decision supported by the data, then it is not of consequence.70 Similarly, a reevaluation of scientific rigor and evidence levels could transform a checkbox mentality and establish the different research methodologies as complementary, answering different questions, and not classified in hierarchies.26,71

In a tiered registry model, those sites in the outermost tier (where the registry would be used mainly for local quality improvement) might collect only a common minimum data set; the inner tiers would provide more and more detailed data in return for rights to use the database.72 Far too many data are collected in general, and only a fraction is finally published. This is not only costly but also indirectly affects the quality of more critical data.23 Outcome assessments may depend on a small number of findings on the primary end point so that those data will require intensive monitoring, but covariate data are typically less important and, therefore, require a lower level of certainty about accuracy: data, for example, concerning date of birth/age, other illnesses, and concomitant treatment unrelated to the disease being studied.70 This, in turn, will lead to better data protection measures if we consciously prioritize and limit the amount of data collected.47,74

Monitoring should focus on the correction of systematic errors rather than individual ones (which is the focus of traditional source data verification associated with clinical trials).75 Apart from the improved focus on critical-to-quality issues rather than all issues, this will also allow research to avoid some of the costs associated with traditional monitoring. Query-driven monitoring (centralized assessment of systematic trends) can result in cost savings between 3%–14% for smaller studies and 25%–35% for large studies.76 In a cardiovascular outcomes simulation (assuming 5000 patients, 587 sites), the cost per patient of a pragmatic study was $8000 (compared to $22,000 in a randomized controlled trial).77

In summary, the key points are as follows: (1) how closely a registry approximates standard clinical practice (procedures that do not pose more than minimal additional risk or burden to the safety of the subjects) and thus capture real-world data and (2) how simply a registry can be organized and conducted to maximize participation and to ensure sustainability over the long term. The nine PRECIS-2 (Pragmatic-Explanatory Continuum Indicator Summary 2) domains (Table 3) were designed to inform researchers on generalizability: how well a protocol matches real-world, standard clinical practice, and our observations were structured in this way (Table 2).78,79 The nine domains can be compared and contrasted with our practical experience in the development of the TREO registry described in Supplemental Material (Appendix 2).

Finally, is a registry easier and less costly to conduct than a clinical trial? There has been a lack of standards for conducting and reporting methods and results which mean that, in the past, registries were easier to set up simply because they had evolved in parallel to traditional research structures and standards were not applied consistently.39 Registries starting in the current regulatory and administrative environment face the same complexity and costs as any other type of research. The challenges we faced in organizing this product registry provided the impetus for this article.

### Table 3. Nine domains of the Pragmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2).

<table>
<thead>
<tr>
<th>Study domain</th>
<th>Questions that affect the external validity of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility</td>
<td>Do inclusion or exclusion criteria mean that patients enrolled will be different to those who are not?</td>
</tr>
<tr>
<td>Recruitment</td>
<td>Does the study mean that treatment criteria are changed in any way?</td>
</tr>
<tr>
<td>Setting</td>
<td>Are all users participating? What distinguishes an institution that participates in the study from one that does not?</td>
</tr>
<tr>
<td>Organization</td>
<td>How different are the resources, provider expertise, and the organization of care delivery in the study compared with usual care?</td>
</tr>
<tr>
<td>Flexibility in delivery</td>
<td>How different is the intervention compared with usual care? How much variability is tolerated in the intervention?</td>
</tr>
<tr>
<td>Flexibility in adherence</td>
<td>How is compliance ensured compared with usual care? Will the study try to improve or alter compliance?</td>
</tr>
<tr>
<td>Follow-up</td>
<td>How different compared with usual care? Will the study alter patient or physician behavior?</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Is it clinically meaningful? Does it need non-typical training to assess?</td>
</tr>
<tr>
<td>Primary analysis</td>
<td>Are all data and all patients included in the analysis of the primary outcome?</td>
</tr>
</tbody>
</table>
By sharing this experience, we hope to contribute to the better use of registry research and raise awareness of the need to distinguish registries from clinical trials.

**Recommendations**

Regulators should simplify and streamline the demands on registries by considering them as low-intervention or non-interventional clinical studies in the framework of pragmatic and large, simple trials and reduce the burden of multiple ethical approvals and costs (Table 4).\(^{80}\)

If the defining difference is that a registry cannot be confirmatory, then it should at the same time be clear that a subsequent confirmatory study can be “nested” in a registry.\(^{81}\)

Consent is an important and sensitive issue, but certain flexibility can be incorporated by establishing consent to data collection (rather than treatment) and defining points of enrollment after treatment (e.g. when emergent). New technologies might even allow a patient to consent and grant data access directly to a sponsor: “mak[ing] all patient data the patient’s by default.”\(^{74,82}\)

Researchers need to guard against overly complex protocols inherited from early-stage clinical trials that result in more study procedures for both patients and health-care professionals, unnecessary data points, and larger case report forms.\(^{83,84}\) Thoughtful review of clinical investigation plans should ensure standardized data collection to facilitate comparisons between the findings of different registries.\(^{46,61,85}\)

The protocol should also use a quality-by-design approach that prospectively defines what quality means in the context of the registry as well as which elements are critical and which are not. The clinical investigation plan should also anticipate how data will be monitored and explicitly justify the design, especially if departing from standard clinical trial elements (e.g. an overall purpose instead of such as primary and secondary

### Table 4. Recommendations.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Registries should be considered in the regulations as observational, long-term, real world with comparison to low-intervention clinical trials and non-interventional clinical studies in the framework of pragmatic and large, simple trials. Regulations should define how registries might be conducted more easily.</td>
</tr>
<tr>
<td><strong>Eligibility</strong></td>
<td>Standards should make special consideration of the inclusion of outside-IFU, custom-made devices, and emergency treatment cases in registries. Consider changing the focus of the registry to the device from the patient. Establish the difference between consent to participation and consent to treat to allow, for example, the inclusion of emergency cases. Report (or estimate) registry participation in relation to total device exposure to gauge how representative the data set is.</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Registries should give an indication or evaluation of how representative the patient cohort included is compared to those not included (at least, an estimate of the total number of patients not included that might have been eligible).</td>
</tr>
<tr>
<td><strong>Organization</strong></td>
<td>Registry clinical investigation protocols should define the characteristics that make it a registry and the nature of the registry holder. Registry scopes should be wider to allow for, for example, different configurations and custom-made devices in the same project.</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Protocol and clinical investigation plan writing should use quality by design elements to identify critical-to-quality points (which must be as close to error-free as possible) and broader “spaces” with greater flexibility and tolerance of error. Design quality and critical issues such as data protection into the clinical investigation plan. Design should include considerations to maintain simplicity, minimize cost, and include contingency plans for sustainability (changes in device, sponsor, etc.).</td>
</tr>
<tr>
<td><strong>Governance</strong></td>
<td>Greater use of centralized monitoring and statistics-based reviews should be used to identify systematic errors (shift from the model of source data verification to risk-based monitoring).</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Include open-ended and mixed retrospective/prospective designs in registry description. Registry design should include flexibility in the definitions of end points and sample sizes depending on the objectives of the research. A registry will always be observational but confirmatory studies can be conducted using the registry as data source.</td>
</tr>
<tr>
<td><strong>End points and sample size</strong></td>
<td>Establishing a 30-day postimplant (or discharge) limit for collection of all adverse events, thereafter only complications (events relevant to the index procedure). Registry end points should not require additional safety reporting. What adverse events are relevant to each registry should be defined in the clinical investigation plan and the total time frame should be considered to avoid overreporting.</td>
</tr>
<tr>
<td><strong>Publishing</strong></td>
<td>Adherence to standard reporting with specific consideration for future metaanalyses.</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Establishing a 30-day postimplant (or discharge) limit for collection of all adverse events, thereafter only complications (events relevant to the index procedure). Registry end points should not require additional safety reporting. What adverse events are relevant to each registry should be defined in the clinical investigation plan and the total time frame should be considered to avoid overreporting.</td>
</tr>
</tbody>
</table>

IFU: instructions for use.
objectives). The protocol might be flexible enough to allow for different levels of participation; any obligatory participation might require only a minimal data set whereas interested investigators might provide more.

Most trials are limited by time (enrollment, follow-up, etc.) but a registry might have no such limitation and be open-ended. Medical and scientific societies can support registry governance by providing the ongoing infrastructure to sustain registries over long periods of time even though manufacturers and individual devices might change. Cost is a major factor in registry sustainability and data sharing and interoperability could reduce operation costs by eliminating the need for manual chart abstraction and common registry infrastructures could allow single capture of common elements such as demographics. Incentives need to be both scientific (investigators can feasibly expect to use the data themselves; reciprocity) and financial (to cover the costs in both time and resources) but may also constitute a quid pro quo for reimbursement. It has been suggested that registries may even be a source of revenue.

The amount and frequency of related publications will help benchmarking in the sector, encourage greater acceptance of innovation, and promote a culture of data sharing. Given the predominance of product registries in the endovascular field, we urge adherence to reporting standards to allow useful comparisons with a view to linking data, establishing meta-analyses and a systematic review-like approach in our specialty.

Existing registries can and should be used more beyond the specific device-related objectives; this should help to avoid duplication of efforts and inefficiencies by sharing data, ensuring transparency, and standard reporting across registries; guidelines for gatekeepers to data sources (not just public bodies but private companies) and a registry specifically for registries would go some way to achieve this aim and might help to distinguish them from trials. Given that many researchers participate in several registries, this needs to be addressed at the time that protocols are drafted to ensure the validity of results from individual registries and to prepare for data sharing and larger meta-analyses. Specialists can help by trying to adapt their respective standard practices to the wider international community and strive for cross-sector alignment with common protocols for patient follow-up and surveillance as well as harmonization of investigative site standards. With regard to safety reporting, centralized, risk-based monitoring is required to avoid too many data and too much workload obscuring relevant information.

Institutional review boards and ethics committees need to be more sensitive to registry methodology, to facilitate simplicity, and not impose a confirmatory design when the research question is best answered using a registry. Hospital administrations might also need to accept lower remuneration reflecting the relative simplicity of the research when compared to clinical trials.

Discussion

We initially questioned the sense of continuing to use the term “registry” when (for all practical purposes) what we were obliged to conduct to fit in with the regulatory requirements was a confirmatory study (Appendix 2 of Supplemental Material). However, it is worthwhile trying to preserve the concept of registries and to resist the encroachment by clinical trials while at the same time striving for improvement. At risk are the advantages of registries and, worse, seeing medical devices become victim to Eroom’s law (a backwards Moore’s Law) that has made drug discovery slower and more expensive despite technological improvements. Scientific evaluation of surgical innovation is more difficult and needs to be considered separately. It took 20 years for randomized trial data to demonstrate the safety and efficacy of laparoscopic cholecystectomy, by which time the procedure was already standard practice worldwide.

Both clinical trials and registries are essential and complementary elements of any “cycle of therapeutic development,” and the strengths and weaknesses of each need to be recognized. Despite disparities in definitions as reported in the literature, a registry is a clinical investigation that involves a long-term, systematic, and organized observational process of collecting data that should be simpler to conduct than a clinical trial. Medical devices are significantly different from pharmaceuticals because of factors such as product life cycle, operator experience, and patient anatomy, and they have specific safety considerations; the regulations and standards governing them, therefore, need to be written with these differences in mind. There have been calls for novel trial designs and analyses to complement clinical trial data with real-world data but registry methodology does not need to be reinvented, just refined, and accorded. Researchers need to keep designs simple and pragmatic. Regulators need to provide a suitable legal environment.

This article reflects the experience of the steering committee of a single product registry (Appendix 2 of Supplemental Material), so it is obviously limited and may not represent other registry organization and development. However, each of the investigators has extensive research experience with other devices, sponsors, and conditions. This article attempted to distill and transmit that collective experience in the hope of contributing to better research in the future. Finally, there is an underlying weakness in the concept of real-world evidence. The differences in the clinical settings between institutions and countries mean that it is not an unproblematic term and may compromise the
objective of generalizability and external validity.\textsuperscript{98,99} Furthermore, despite the desire to embed research in everyday clinical practice, it does need to be distinguished because the latter introduces competing interests (generalizable knowledge, financial compensation, and professional recognition) in the physician–patient relationship.\textsuperscript{100} However, as Godwin et al.\textsuperscript{101} warned: “the attempt to achieve methodological purity can result in clinically meaningless results, while attempting to achieve full generalizability can result in invalid and unreliable results; achieving a creative tension between the two is crucial.”

Conclusion

Both clinical trials and registries are essential and complementary research methods, and the strengths and weaknesses of each need to be recognized. The specific characteristics of registry research deserve to be acknowledged and safeguarded in the regulations governing clinical investigations with medical devices.

Acknowledgements

Thanks to Eoin McGrath of the European Society for Blood and Marrow Transplantation (www.ebmt.org) and Danielle Giroud of MD-CLINICALS SA (www.md-clinicals.com) for their input and advice.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The TREO Registry was funded by a grant from Bolton Medical (now Terumo Aortic). The authors have no conflicts of interest relative to this article; P.B. is an employee of Terumo Aortic. The content of this article does not reflect the official opinion of Terumo Aortic. Responsibility for the information and views expressed therein lies entirely with the authors.

ORCID iD

Patrick Bohan  https://orcid.org/0000-0002-1148-2645

Supplemental material

Supplemental material for this article is available online.

References


89. Neugebauer EAM and Stausberg J. Was Register leisten können und was nicht. Der Unfallchirurg 2016; 119: 493–500.


