42 CHAPTER

Measuring Outcomes in Orthobiologics – Registry

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INTRODUCTION

The field of regenerative medicine is growing rapidly in both clinical application, and patient desires for more "physiological" and precision approaches (Murrell et al. 2015, Gameiro et al. 2018). The value of a treatment can be simply defined as the outcome divided by the cost (Gray and Abbasi, 2007). Determining the clinical value of orthobiologic treatments, or injections consisting of cells, and or proteins collected from the patient, processed, and then used as treatment for underlying orthopaedic pathology is not easily defined, as these factors are commonly missing from the majority of current publications in the arena today. This includes quality measures, characterization of injectate, cost, adverse events, and long-term follow-up (Marenah et al., 2019). Therefore, there has been a great effort by stakeholders to increase available evidence, based on clinical outcomes to provide a potential road map on delivering quality for facilities providing orthobiologic therapies. Additionally, to provide 'real-world' feedback on safety and efficacy of these treatments, observational practice registries have emerged in these clinical environments throughout the world (Chiauzzi et al., 2015, Bai et al., 2016).

A patient registry is defined as 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 a predetermined scientific, clinical or policy purpose(s) (Gliklich et al., 2014, and Arts et al., 2002). Specific to the topic at hand, various orthobiologic treatments, such as platelet-rich plasma (PRP), stem cells, autologous conditioned serums, use, have become more mainstream (Murrell, et al., 2015). Physicians utilizing these techniques occasionally monitor the treatment outcomes through both clinical outcomes and patient reported outcome measures (PROMs) (Centeno et al., 2016; Gagnier 2017; El-Daily et al., 2016; Gobbi et al., 2021; Schneider et al. 2020; Melo et al., 2020; Badsha et al., 2020; Betancourt and Murrell, 2016). Tracking treatment outcomes optimizes healthcare value by removing non-useful treatments or care at a lower cost (Makhni et al., 2015; Jain NB et al, 2013; Virani et al., 2013). The great impact is that registry data can aid in the development of shared guidelines or treatment protocols for physicians utilizing those specific treatments based on outcome and observation (James and Savitz, 2011; Parker and Vitelli, 1997). Alternatively, assessing the effect of one parameter at a time, require a much longer turnaround time before useful information is released into the public domain (Choinière, et al., 2017).

Public/national registries and private/industry registries are more focused on decreasing cost, whereas, many involved in the regenerative medicine movement, believe that more individualized treatment

focus is required to treat underlying causes of disease. Specifically, for the delivery of orthobiologic treatment(s) and platforms, the focus is to cure or restore, and not merely manage (Mason and Dunnill, 2008; Lecluse et al., 2009). Although many public/national registries focus on a specific disease or disorder, and usually have a high participation rate as they include the majority of a nation's diverse population, but some may lack local specificity to selected population that may result in not being able to apply findings to separate, diverse populations (Allen et al., 2008). The advantage of collecting patient outcomes for cellular based products at the clinical level thus provides an effective feedback tool for doctors examining the effects of orthobiologic treatment, based on observational data that is reflective of the population being treated (Choinière, et al., 2017).

A clinical outcomes registry is an organized system for collecting patient outcomes as data points relevant to the effect of treatment on pathology or injury. A key benefit of this type of registry is its agility. The registry can quickly identify underperforming products/treatments in use for a specific facility by linking the product use/technique to patient reported outcome measures (PROs) and adverse events (AEs). For the field of orthobiologics, this is critical, as data and information about the efficacy of treatments is growing, but not fully known (Centeno et al., 2016; Gagnier 2017; El-Daily et al., 2016; Gobbi et al., 2021; Schneider et al. 2020; Melo et al., 2020; Badsha et al., 2020; Betancourt and Murrell, 2016; Centeno et al., 2011; Centeno et al., 2015).Therefore, the PROs (Nelson et al., 2016; Gobbi et al., 2021) can be used in conjunction with costs to compare (using cost-benefit analysis such as quality-adjustment life year (QALY)) and assign value to treatments (Gray and Abbasi, 2007; Wicks et al., 2016). The registry enables an almost immediate treatment feedback which allows practitioners to make adjustment(s) to treatment protocols as needed. Also, the registry provides critical general patient flow or system process information, including recovery process, that is under reported in the literature (Makhni et al., 2015). Moreover, with a clinical outcomes registry there is no need to wait for slow output/publications that are commonly associated with larger public/national and private/industry registries (James and Savitz, 2011).

The clinical outcomes registry provides real-time, localized data about the population undergoing the direct treatments/products of the facility. With this data in hand, the facility can make informed and rapid choices about how to improve treatments/protocols based on their specific patient flow rather than inferring from results derived from a population sample.

For cellular-based and conventional based registries alike, treatments can be organized into four categories: (1) non-operative and non-interventional, (2) non-operative and interventional, (3) operative and non-interventional, and (4) operative and interventional (ex. surgical injections) (Gameiro et al., 2018). Most private/industry-funded registries focus on operative and non-interventional therapies and are potentially under-developed on non-operative intervention (McLean 2010). Facilities using biologic therapies to treat musculoskeletal disorders need comprehensive descriptions of treatment outcomes for each category (Gray and Abbasi, 2007; Wicks et al., 2016), yet other registries do this in a general way within pre-set boundaries and descriptions that lack specificity about the intervention (James and Savitz, 2011). The clinical outcomes registry model consists of how well characterized products are administered that are specific to the facility, in conjunction with adaptable processes to alter treatment pathways in response to unfavorable patient responses.

In the context of the emerging areas of patient registries in routine clinical practice in combination with regenerative medicine, the aim of this didactic chapter is to describe a proposed implementation of a clinical outcomes' registry within a clinical setting for conventional orthopaedics and regenerative medicine.

FACILITY FOCUS

Localized registries contribute to involved facility by addressing quality issues that can be determined, assessed, and solved through the implementation of a clinical outcome registry. One of the biggest values that results, is to be able to quickly assess and change treatment protocols as needed and to process feedback regarding the facility in reference to the specific population and treatment strategies (Figure 42.1).

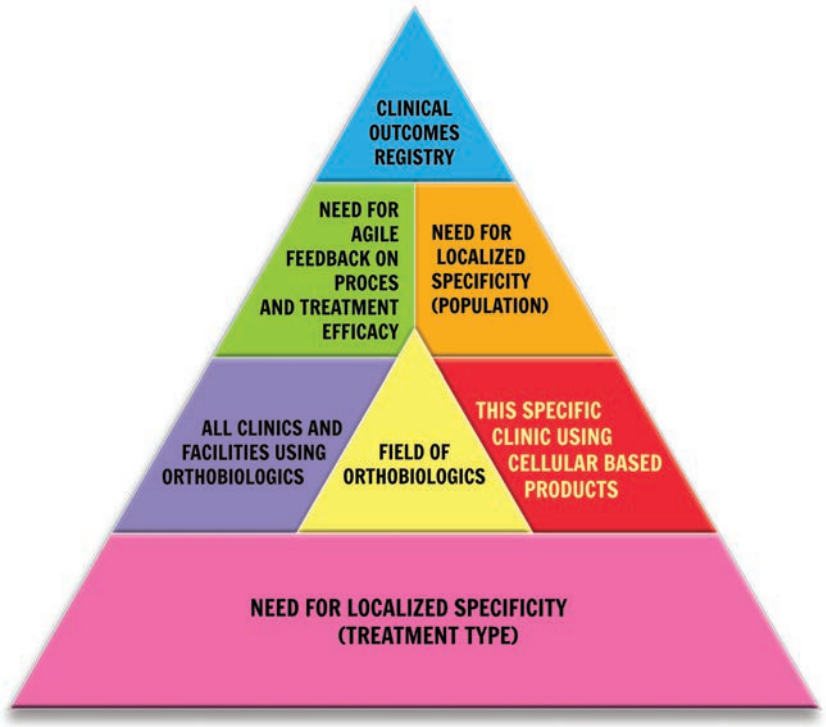

FIGURE 42.1 Interaction between limitations overall and local challenges.

Without a registry, in general, facilities lack an efficient system to incorporate treatment and process feedback into a facility's patient flow and treatment plans. Without general feedback regarding the various product efficacy, systematic adjustments to treatment plans cannot be made for various musculoskeletal disorders, or is done so based solely on the intuition of providers. By utilizing feedback to eliminate ineffective treatments for specific disorders, then the costs of care can be impacted, in many instances decrease, and be optimized (as seen with Intermountain Healthcare's work to eliminate

ineffective treatments which lowered the costs of overall healthcare) while benefits increase and in turn increase the value of specific treatment options (James and Savitz, 2011). Facilities using conventional and or cellular based products can benefit from a clinical outcomes registry which would allow for more agile feedback an improved ability to create and improve effective treatment protocols (Gay and Abbasi, 2007; Nelson et al., 2016; Wicks et al., 2016).

Although large, public/national and private/industry registries provide useful evidence about patient outcomes for various treatments, they lack specificity to a facility's specific population and treatment strategies (Allen et al., 2008; Lecluse et al., 2009). A facility that utilizes innovative orthobiologic or conventional treatments and products require patient outcome data specific to their population that is being treated to be comprehensive in their care delivery. Specificity, regarding treatment protocols, allows for more detailed assessment about the treatments and avoid unimportant information from being documented.

CHALLENGES

Despite its purported advantages, there are many challenges associated with the implementation of a clinical outcome registry including costs (i.e. time, money, resources), coordination amongst multiple practitioners and clinic staff, and managing various conventional as well as cell-mediated treatment strategies (Gliklich et al., 2014). The first challenge associated with the implementation of the clinical outcomes' registry is the overall cost, including time, money, and resources (Korir et al., 2016). Registry implementation requires efficiency in order to minimize related costs for the facility. Additionally, coordination amongst multiple practitioners and clinic staff may be a hindrance to the implementation and initial use of the clinical outcomes' registry, therefore a stepwise approach should be adhered (Latham et al., 2012).

Once the implementation plan is clear, and executed, the next crucial step is defining the roles of all stakeholders involved. The development of detailed guidelines and procedures to ensure staff using the registry daily are well versed in their roles. The final step, is to ensure that all parties are well versed in the management of various conventional as well as cell mediated therapies, as this can be a major challenge for the facility. Every member of the team is a representative of the program, and thus needs to be able to communicate effectively about every and all treatments, at least at a basic level, even if they are not directly involved in clinical care. This is extremely important, and detailed training of the procedures and processes are critical. This is how an innovative cell based/conventional treatment registry differs from most current registries, in that mainly the latter focuses more on surgical intervention versus treating the whole person. An ecosystem of excellence, a distributed level of responsibility needs to be created and established to ensure that all the cell mediated and conventional therapies have a very clear and understandable detailed framework to manage the wide array of factors and requirements, such as the frequency of treatment, to ensure smooth transitions between the various stages of treatment (assessment, qualification for treatment, conservative therapies, interventional therapies, surgical treatment, rehabilitation).

The most important component of planning a registry, is to have a clear idea and understanding about the outputs of the registry, and what the vision and mission are for the facility. When there is clarity

of purpose, and having completed a detailed outline of the program, the directives are easy to follow, and all involved understand their roles and responsibilities, as well as deliverables. Having a very high-level view concerning the output of the registry, and what is expected especially in the very beginning of data collection, will ensure that the what is created is actually useful in the end. For example, if entry participation into the registry for a particular cohort is less than 90-95% in the beginning, the likelihood of having complete datasets at minimum follow-up of 2 years is very unlikely, as atrophy of follow-up is very common (if less than 70% participation at follow-up, unlikely that most peer-reviewed journals will accept the manuscripts for publication) (Ayilara et al., 2019).

REGISTRY OVERVIEW

The primary purpose of the clinical outcomes' registry was to objectively assess, analyze, and maximize patient-centered outcomes for surgical and non-surgical management of knee, shoulder and foot and ankle musculoskeletal disorders amongst the patient population. The secondary objective of the registry was to use clinical data to record the efficacy and safety of approved conventional, interventional, and biological treatments order to improve their performance and direct future improvements in patient care. The registry is necessary to monitor both the natural history of orthopaedic pathologies occurring in the general population, as well as short-term and long-term patient outcomes associated with these pathologies and contemporary treatment options. The registry is comprised of three sections: i) registry framework, ii) the patient cohorts, and iii) quality assurance (Figure 42.2). In the first section, the general recruitment process of patients into the registry was documented and communicated using diagrams and step-by-step instructions. In the second section, the four diagnostic cohorts are created to document respective symptoms, treatments, and PROs to compare patients within each cohort. In the third section, the descriptions for how the data from the registry would be used to evaluate the quality of treatments, auditing treatment finances, or identifying issues to be solved through required and appropriate training.

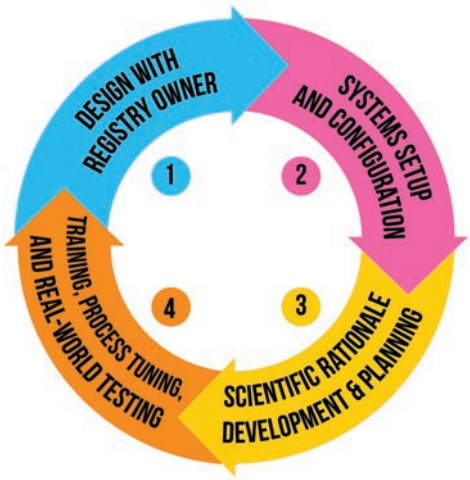

FIGURE 42.2 Structural components of the registry. Registry Framework, Registry Cohorts, and Quality Assurance and Data Management.

IMPLEMENTATION PROCESS

Implementing a clinical outcomes registry within an existing sports medicine and orthopaedics facility, with a short history of administration of orthobiologics can be broken down into four steps (Figure 42.3): (1) designing the structure of the registry with the intended owner, (2) utilizing previously published literature about conventional orthopaedics/sports medicine, and overlap with regenerative medicine to develop scientific rationale for data collection points and methods for cell-mediated treatment within the registry, (3) setting up and configuring the system within the facility, and (4) training all medical staff that would be involved with patient flow throughout the registry process, making small adjustments based on the facility's needs, and testing the registry with the population that will be participants in the future (Hudelson et al., 2013).

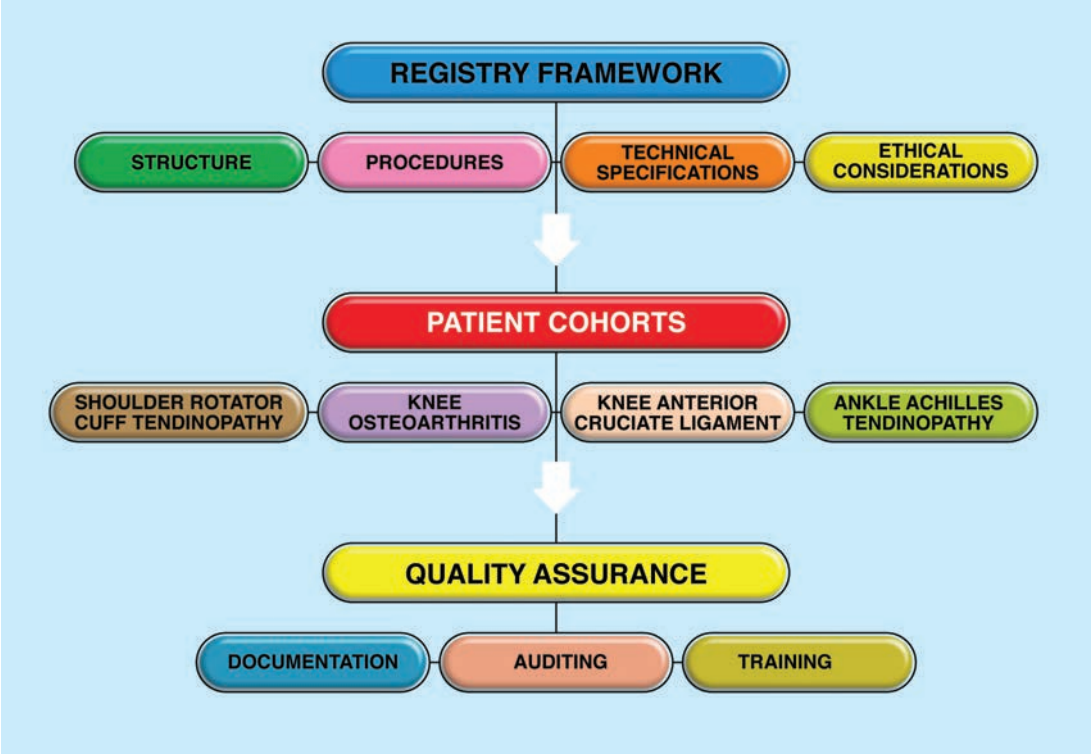

FIGURE 42.3 Overview of implementation process.

Design

The first stage of building the registry consisted of a draft design. According to the aforementioned definition, a registry consists of "an organized system that uses observational study methods to collect uniform data that serves a predetermined purpose," therefore, registry designers need to extensively plan and communicate with registry owner(s) to establish the scope and scale of the registry (Hudelson et al., 2013). Within these interactions/conversations, preliminary work is conducted to connect the

registry with the overall research program goals and design observational study methods that accurately allow for the purpose to be fulfilled through the uniform data (Hudelson et al., 2013).

SCIENTIFIC RATIONALE

Development of the scientific rationale for the registry required a solid understanding of what the registry owner (a clinician in this instance) wants to know about their patients, treatments, and outcomes (Latham et al., 2012). The registry needs to have collection methods and data items that are applicable to the specific conventional therapy, as well as regenerative medicine treatments intended to be used. Therefore, registry information about these treatments can be derived from the current literature about conventional treatment, as well as orthobiologics. Understanding that the registry structure is in a cohort format, each grouping had specific outcome measurements that were unique to those musculoskeletal disorders. Therefore, the recovery goals through various treatments were specific to each cohort. Additionally, literature relevant to each cohort needs to be analyzed to determine the relevant diagnoses, the treatment pathways for the cohort, the most appropriate follow-up intervals, and which outcome measurements are to be used to establish treatment efficacy. Each cohort's context within literature and plan for diagnosis, treatment, and analyses will need to be thoroughly documented and made available to a broad range of registry stakeholder(s) throughout the proposed development period.

STANDARDS AND PROCEDURES

A number of standards operating procedures to be created are necessary in order for the registry to maintain its integrity and to align with local regulatory and international best practice guidelines for human subjects research and good clinical practice. In designing the registry, informed consent, data protection, marketing practices, and the credentials of investigators need to be emphasized. In design of the registry, informed consent should be approached as an opportunity to communicate with patients about the nature of the registry, manage their expectations, their right to refuse or withdraw, and prepare them for further communication. Data use and protection is one area of particular concern by regulators regionally/internationally, and specifically for the specific patient population, and detailed procedures-mentioned in the Informed Consent-are to be developed in order to allay fears related to data security.

Coordination between the registry designers and the clinicians are crucial during the system setup and configuration step of the implementation. Identifiable data is usually planned to be maintained electronically on a secure server locally, and all identifying information such as name, date of birth, email, or phone needs to be removed from any data prior to transfer of the data to all approved remote sites. The physical terminal server should be located at the facility and backed up daily at approved locations. Regular quality control audits are to be conducted to ensure data quality is at an adequate standard for clinical research. Registry level completeness audits should be performed every two (2) weeks until the benchmark 90% of potential patients is reached and performed monthly once above the benchmark.

As mentioned before, coordination amongst multiple practitioners and facility staff may be a hindrance to the implementation and initial use of the clinical outcomes registry. Detailed descriptions of each person's role within the registry documentation process need to be provided in order to prevent important information from being neglected. Additionally, precise coordination between the registry support team and the local team will prove difficult. Therefore, in-depth training and fine tuning for clinicians, nursing staff, clinical support, admin staff, and the registry support team is crucial for the success of the final implementation step. Online, in-person, and remote support can be used to deliver ongoing training and process correction. Additionally, training from the registry support team needs to be provided ongoing, to ensure that the facility understands, and are able to proficiently input data into the registry. Depending on the healthcare facility, it's clinical capabilities, staff size, etc., the specific roles of staff can be adjusted and fine-tuned to promote a smoother process.

Finally, testing the efficacy of the registry itself within the new clinical environment is only possible through real-world testing. Once the training is completed and the registry fully created, then a small population of patients can be added to the registry to analyze the process flow. Starting with a small, pilot group to account for unforeseen adjustments to be made without disrupting patient flow in involved departments. After the clinicians and registry support team are content with the overall registry and patient flow, the registry can be fully implemented with all patients.

EVALUATION

The effect of the change in clinical practice can be assessed through quality metrics associated with the registry itself, such as the accuracy of the data linked to supplementary data (e.g. clinic documentation). Once the registry completes its implementation phase and enters a pilot period to confirm data collection processes and user feedback. Initial findings usually indicate missing data in key areas that can be rectified by refining data field definition, placement within the operating system, linkage to external supporting documents and response options for users to select during data entry. Improvements to clinical practice were assessed through data quality assessment, patient outcomes relative to pre-specified treatment success criteria, as well as safety relative to external sources for benchmarking. In addition, the experience of users can be assessed at the end of the initial pilot period (3 months) and changes to clinical practice over the course of the registry implementation are noted in a documentation manual to provide context to data analysis in the future.

The key impacts of the registry implementation have been to i) redefine criteria for treatment success and failure within the area of biologic/conventional treatments in musculoskeletal practice (Gliklich et al., 2014), ii) instigate between-practitioner discussion and documentation regarding standardizing treatment pathways (James and Savitz, 2011), clinical handover processes and shared decision-making with patients (Gagnier, 2017) and iii) act as a catalyst to target deficiencies in staff knowledge and skills in the areas of patient management and interaction (Wicks et al., 2016), clinical documentation and administration processes (Chiauzzi, et al., 2015).

LESSONS TO BE LEARNED

The registry implementation established a series of processes within the facility, linked to the latest evidence, to identify patient outcomes with respect to treatment of musculoskeletal conditions. The success of introducing a registry in this environment will depend on the organization of the clinic and the leadership of key stakeholders within the process, both in the design and the practical translation of data collection processes to action. Standardization of treatment pathways are required to anchor data collection processes and provide meaningful feedback on patient outcomes.

The change process can be hampered by a lack of interoperability between electronic data systems, issues of standardization of definitions that can lead to duplication of data collection between staff groups and the definition of treatment in the context of nonoperative management, conventional, and biologic therapy in the context of following up patients at predefined time periods. To combat these issues during implementation, communication needs to be formalized with all stakeholders earlier in the planning process to gather feedback on data collection logistics from the clinic staff as part of the design phase.

However, there are general constraints and limitations on the effectiveness of a clinical practice registry. First, the limited access to the owner or stakeholder can prevent smooth communication between registry staff and support. Second, communication access depending on the location can inhibit the ease of communication between registry faculty and support. Third, the differing levels of knowledge and experience within the clinic environment incorporates multiple stakeholders into the patient flow through the registry which can prove a hindrance and limit the effectiveness of a practice registry.

Nevertheless, the implementation of a practice-based patient registry can enable clinicians to not only keep track of their own performance, but to contribute to the evidence regarding emerging therapies in a systematic manner by monitoring patient outcomes. In addition, the introduction of a practice registry can provide a platform for monitoring treatment safety and efficacy in the context of conventional nonoperative and operative treatment, as well as biologic therapies in musculoskeletal medicine and to contribute to ongoing discourse regarding best value treatments for a range of disabling conditions.

The aim of this didactic chapter was to describe the implementation of a clinical outcomes registry within a clinical setting for conventional nonoperative, operative, and regenerative medicine within a musculoskeletal context. Through a detailed explanation of the implementation process, a registry style can be adapted to support musculoskeletal facilities to transition from purely conventional and interventional, but to also include regenerative medicine services worldwide. The utility of this chapter is to outline the steps of establishment of a treatment registry from planning to implementation. With a good plan in hand, not only is creation, implementation, and execution possible, but also the steps of making the necessary adjustments to ensure the registry is able to serve its full purpose to address quality issues, feedback, agility and specificity. Future work should examine the quality of the data held by the registry and begin to interpret the patient data captured during its pilot phase.

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CONFLICTS OF INTEREST

GM Founder and Partner of Data Biologics

CR Founder and Partner of Data Biologics

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