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RegenMed partners with various healthcare stakeholders around the world to develop and execute registries having various levels of complexity. The following observations and suggestions derive from that experience. They will assist medical societies, foundations and other healthcare stakeholders as they consider the design and execution of real-world evidence ("RWE") registries.

OBSERVATIONS

Risks of Multiple/Mixed Objectives

Without a clear and realistic definition of its principal objective, the effectiveness of any registry is impaired.

A registry [1] may have one or more of the following objectives:

- Safety and efficacy of specific products.
- Safety and efficacy of specific procedures.
- Compilation of conditions susceptible to primary or adjunct therapies.
- Specific types of regulatory submissions: IND, IDE, 510-K, PMA, post-market, other. [2]
- Advancing the science of a specific medical sub-discipline.
- Support for clinical decision-making.
- Establishing standards of care for particular indications or treatment protocols.

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1 As indicated below, the registry sponsor may wish to consider several RWE registries, which provide value individually as well as in the aggregate.

2 Each of these has its own requirements in terms of level of evidence and other parameters (e.g., Part 11, CDISC or other messaging format) and therefore time, cost and personnel.

There is of course overlap among the foregoing and other possible objectives, but there are also major differences among them which have large implications for the design, execution and ultimate value of a registry.

Incentives and Motivation

Registries – and indeed traditional randomized controlled trials ("RCTs") – often struggle to achieve their potential due to inadequate motivation of clinicians and patients to provide the necessary data in a verifiable, timely and complete manner.

Clinicians

For an RWE registry, clinicians will be called upon to:

- collect data,
- implement data verifiability processes,
- follow-up with patients,
- coordinate with laboratory or other scientific data sources,
- train and oversee existing and perhaps new staff,
- create and maintain documentation.

Clinicians are already overburdened with legal and administrative requirements regarding each of these items. Participating in a proper registry will substantially add to this burden, typically without a benefit commensurate with that additional burden. [3]

[3] Many physicians wish to "do the right thing" and support registries in order to advance medicine. Even for them, however, the realities of everyday clinical practice make meaningful participation impractical.

Patients

The collection of long-term follow-up data from patients is of course a critical part of an RWE registry. There are many dozens of PROMs platforms available, but most fail to drive longitudinal patient compliance due to no perceived value. While an RCT will financially compensate patients, this may not be feasible for an RWE registry where a large "n" value is necessary to achieve statistical significance.

Funding Sources

Registry costs can be considerable, and the registry sponsor is likely to seek third-party sources to underwrite at least some of them. Sources include government research grants, foundations, product manufacturers and distributors, and payers (including self-insured employers and employer groups [4]).

Other Common Challenges With Registries

Burden of Execution

Real-world evidence is derived from the busy clinic. Without minimizing the burden imposed on a clinician and her staff, a registry is unlikely to achieve the necessary amount of verifiable, longitudinal and relevant data. Regardless of financial and other incentives, the minimization of burden involved in registry participation is critical. [5]

Poor Integration of Systems and Processes

By definition, an RWE registry need not involve the cost, duration and complexity of an RCT. However, for any objective, it will share certain

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4 As but one example, the Health Transformation Alliance.

5 This is particularly true for clinicians, but is also applicable to patients.

requirements – data verifiability, patient-privacy and often consents, robust data analytics, defensible clinical/scientific hypotheses, a study design integrated across pre, peri-, and post- clinical information, longitudinal patient engagement and, of course, funding.

Separate process categories which should be integrated include scientific, clinical, commercial, communications, IT and data analytics.

These basic requirements have major implications for efficient, integrated systems and processes – not only to minimize cost, but to avoid errors and allow scaling.

Balancing Flexibility With Standardization

Most PROMs and other components of registry "protocols" are one-size-fits-all, with little or no flexibility for the clinician to adapt them to her specific practice. This need not be the case, especially in the context of RWE registries. Modern technical platforms allow the design and implementation of registry protocols which can be customized to the specific clinical protocols of the participating practitioner.

The Implications of "Real-World"

In establishing its principal objective for a "real-world" registry, the sponsor will benefit from carefully defining the term "real-world".

"Real-World" For The FDA

The Cures Act and associated FDA publications provide extensive guidance on what can be characterized as real-world data and evidence for purposes for regulatory decision-making. Taking these requirements as a whole, the development of such FDA-compliant RWE implies costs, processes, personnel

and timing which often would not be significantly less than traditional RCTs. [6] This will be particularly true in the case of biologics and other "regenerative medicine" therapies, which can involve systemic effects and mechanisms of action dependent on individualized measures. [7]

Thus, establishing an RWE registry compliant with FDA requirements will have significant implications in terms of cost, personal and processes.

"Real-World" For the Real World

There is also a medical/scientific "real-world" which deserves consideration – that of the busy orthopedic surgeon and other practitioner, and of their patients. This involves an assessment of clinical decision-making, product evaluation, provider selection, reimbursement, time and cost burdens, staff and laboratory constraints, and other realities. [8]

This real-world is necessarily less rarefied and "messier" than that of the FDA's; however, it is arguably the more important "real-world". It is where the vast majority of the over one billion annual patient/physician interactions take place. It is also where the registry sponsor can make a product-agnostic, substantive and sustained impact by adapting the best practices of RCT methodologies to the realities and needs of the typical clinician and his patients.

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[6] On the one hand, this is understandable given the FDA's statutory mission. On the other hand, it is unlikely to have been the intent of Congress in passing the Cures Act.

[7] For example, whole blood platelet, concentrated platelet,, hematopoietic stem cell, leukocyte and other counts.

[8] As pointed out by the Agency for Healthcare Research and Quality, part of the U.S. Department of Health and Human Research, 90% of clinical procedures are based on inferior evidence levels. See the AHRQ's "Registries for Evaluating Patient Outcomes: A User's Guide: 4th Edition".

E Pluribus Unum: Sub-Registries ⇒ Master Registry

At least four major factors argue in favor of multiple RWE registries:

1. In the modern world of personalized medicine, many therapies are by definition specific to the patient's specific glucose, erythrocyte, platelet, growth factor, leukocyte and other "counts".
2. Many therapies currently in common use involve various hypotheses regarding efficacy in the context of concentration levels, activation agents, dosage, injection site, number and interval of injections, and other parameters.
3. The markets for many products used in many treatment protocols are fragmented and unstandardized.
4. The members of a medical society often represent a wide variety of sub-specialties and patient cohorts, for each of which one or more of various therapies are likely to be in use and or of clinical interest.

Nevertheless, the principal initial scientific hypotheses for a specific registry dedicated to a specific treatment protocol may also be relevant to certain "adjacent" therapies. Implementing common protocol elements across various registries will allow the derivation of "serendipitous" as well as initially presumed hypotheses.

ONE POTENTIAL PATH

Determining The Registry's Principal Objective

There are many potential objectives for a real-world registry. Two initial criteria may help define an overarching goal:

What Is Achievable?

A medical society typically is pursuing multiple initiatives, of which an RWE registry will be only one. A sober assessment of the personnel, funding and time available to execute this registry consistent with the society's reputation and standards is an important element in determining the registry's principal objective.

What Will Have The Greatest Impact?

The missions of a medical society will often include one or more of member education, advocacy, and developing standards of care relevant. An RWE registry sponsor will wish its parameters in the context of at least one of its missions. Properly structured and executed, such registries can deliver demonstrable impact in a relatively short amount of time.

Motivations

Merely covering the costs for participating clinicians is often insufficient, and indeed impractical. Far more effective incentives include honoraria, investigator fees, reimbursement for conference attendance and presentations, assistance with publication,[9] provision of part-time scribes, patient education materials, and providing systems and processes which reduce the burden of registry participation.

Designing, funding and reliably executing these incentives give a registry the best chance of success and impact.

[9] Impactful and legitimate publication includes not only peer-reviewed journal articles, but abstracts, conference presentations, data-supported blog posts, patient education materials based on current science.

Proof of Concept

To achieve its objective(s), any registry must properly design and continually implement several scientific, clinical, financial and operational elements. Doing so is necessarily a complex undertaking. It therefore makes sense to begin with a modest "proof-of-concept" phase, allowing the sponsor first to analyze and then improve various elements of its design and execution.

Scaling

Whatever the initial objective and scope of the registry, the registry sponsor will wish to expand its reach. It will also seek to accommodate other objectives. [10] In both cases, carefully designing the foundational elements of the initial registry, especially with respect to systems and processes, will enable it economically to do so.

Funding

The most accessible and significant funding source for the registry is industry – usually manufacturers and distributors. However, self-insured employer groups are also likely to represent significant financial support. [11] In all events, funding efforts will need carefully to balance RWE objectivity with perceived value for the funder.

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[10] For example, an initial goal may be to support decision-making by clinicians seeking to utilize a specific type of orthobiologics in the context of a specific condition. Subsequent or parallel registries could cover other orthobiologics for the same or similar pathologies.

[11] Funding support will be necessary not only for the sponsor's direct registry costs, but also properly to incentivize participating clinicians. These incentives may come directly from the funding source in the form of, for example, investigator-initiated trials, or may be intermediated through the sponsor or an affiliated organization.