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The Role of Observational Research & Patient Registries in Evidence Generation

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The modern healthcare environment is a mosaic of stakeholders, each with remarkably different demands for data addressing product attributes. Neither orderly, nor fully rational, these often conflicting perspectives require access to a portfolio of interventional and observational research designs subserving different objectives, and tiered in importance and timing during the drug development cycle. Increasingly central is the inclusion of observational studies, including registries which **provide insights missing from traditional interventional studies encountered in the course of drug development.**

When properly designed observational studies yield estimates of treatment effect comparable to randomized controlled trials[1], and generate real-world data to support marketing authorization with estimations of costs/resource utilization to inform formulary placement, coverage, and levels of reimbursement. Differentiation of therapy regarding long-term efficacy and quality of life in a more heterogeneous population is more feasible than during a traditional pre-registration program, and a spectrum of clinical endpoints can be incorporated to measure effectiveness and feasibility of use in typical practice settings in comparisons to current standards of care[2].

A Portfolio of Designs

Observational studies exist across a continuum of descriptive, exploratory, and experimental designs (randomized controlled trials) enabling hypothesis generation and hypothesis testing, respectively. These include case studies, cross-sectional studies, case-control studies, serial cross-sectional studies, retrospective cohort designs, longitudinal cohort studies, nested case-control studies, quasi-experimental designs and of course randomized clinical trials[3]. Patient registries are an important component within this armamentarium as they facilitate acquisition of longer-term efficacy and safety data, long-term modeling of healthcare outcomes, and provide insights as to market penetration and prescribing habits for newly introduced drugs, biologics or devices[4].

Additionally, registries and other forms of observational research permit a focus on patient reported outcomes thus capturing a 360°

perspective of the effectiveness of medication/devices along with improvements of quality-of-life measures and costs. Due to the inclusion of more representative patients, with a range of concurrent illnesses and concomitant medications, data facilitate an examination of subgroups that previously may have been undetected in which benefit/risk ratios are enhanced and for which additional investigation in well controlled settings is warranted e.g., phenotypic/genetic moderators of treatment response[5]. Because of the nature of the population evaluated registries particularly facilitate the identification of off label use in potentially new indications, enable long-term safety surveillance and shed insight regarding estimates of comorbidity and concomitant use of other medications used to manage disease states which reflect chronic multiple morbidities[6]. The design of operational research studies and the type of data collected varies by the phase of drug development and the intended final use of the information.

Design Consistent with Objectives

Data Final Use	Drug Development Phase	Data Objective	Study Design
Drug Development Plan	Pre-Marketing	Design of Phase II & Phase III Studies	Natural History of Disease
			Burden of Illness
			Treatment Patterns
			Competitor Products
			Disease Management
	Post-Marketing	Labeling Extension	Brand Usage
		Profiling Competition	Comparative Effectiveness
			Disease Management
			Health-Resource Usage
Regulatory Submission	Pre-Marketing	Supportive Data	Long Term Safety
	Post-Marketing	Safety	PASS (Post-Authorisation Safety Study)
		Efficacy	PAES (Post-Authorisation Efficacy Study)
Reimbursement	Pre-Marketing	Initial Pricing	Comparative Effectiveness
	Post-Marketing	Price Negotiation	Health-Resource Usage

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Why Not Piggyback?

The unique attributes of observational studies – which cannot be replicated in many explanatory trials – bring to question the utility of "piggybacking" healthcare utilization and associated economic questions onto prototypical phase 3 trials. The approach yields a patient population not fully generalizable to those ultimately using the product[7,8]. Additionally, the visit duration and interval encountered in interventional studies for registration studies are constrained; questions referable to efficiency are hobbled by sample sizes which generally are underpowered for healthcare utilization outcomes of interest (e.g., they are not primary to the protocol); the duration of studies within registration programs frequently is too brief to permit access to meaningful longer-term outcomes; and sites may become tentative regarding the acquisition key data points over time if they are not perceived as primary or key secondary questions. Finally, patients transition out of interventional studies for variety of reasons related to safety, efficacy, and convenience. Therefore key data regarding subsequent disease management and patient outcomes are often missing from analyses and modeling. Although questions better suited for observational research conveniently may be grafted onto to pivotal interventional trials given the "built-in" patient population which they provide, the technique may be limited to hypothesis generation to inform subsequent independently designed studies.

Viewing the Data through Different Prisms

The mix of interventional versus observational studies in a development program is reflected by the mix of stakeholders implicated in this process. For example, patients might be specifically interested in outcomes directly relevant to the most troubling sign or symptom of the presenting illness; while payers may focus on physician adoption, coverage, and pricing including reimbursement method. Providers (physicians) often require data within their specific clinical care system to maximize obtaining estimates of healthcare utilization as the most directly relevant method of forming their clinical practice. Indeed, in a development program which must include studies covering the entire drug lifecycle, the planning for observational studies, including registries best occurs at the end of first in human studies in which preliminary descriptions of product characteristics are available.

Drug Lifecycle and Study Types: When to Begin?

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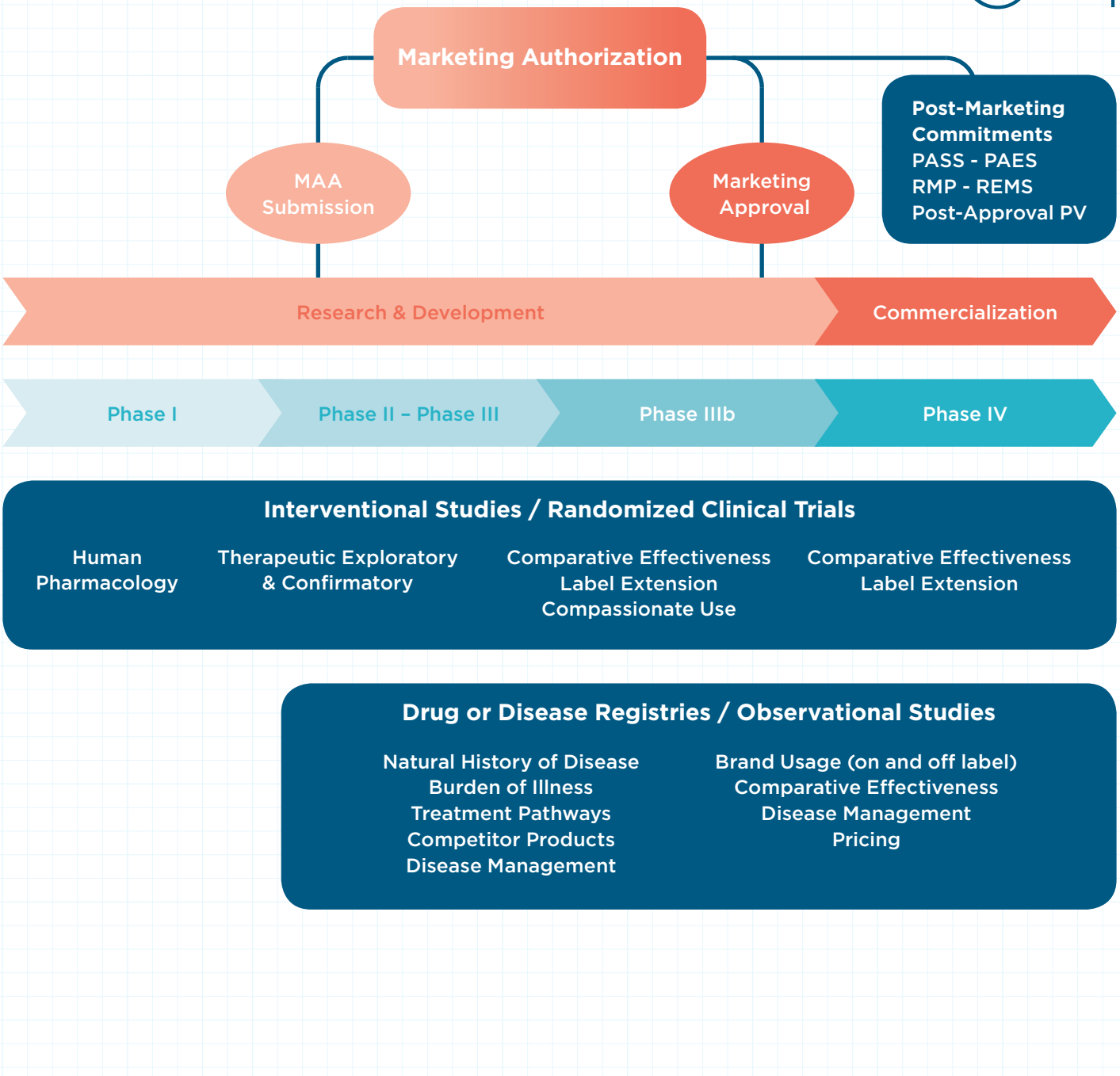

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Designing for Success

A range of designations have been used to capture all of the many variations of observational research which are possible. These include noninterventional studies (NIS) compassionate use programs, registries, late stage research, post authorization safety or efficacy studies, expanded access programs, phase IIIB/IV, risk evaluation and mitigation strategies (REMS), amongst many others. Similar to interventional studies, designing a successful study often requires unique approaches to implementation. Beginning with sound methodology, the importance of steering committees and various permutations of remote clinical monitoring must be acknowledged. Brief protocols (and even shorter case report forms) facilitate participation from physicians and patients who are unacquainted with the demands of good clinical practice (GCP) compliant research as would be awareness of the fair market value for services provided by these sites. Finally knowledge of regulatory approval timelines is essential to optimize study timing. Given the importance of local key opinion leaders, and local sponsor affiliates, inclusion of diverse stakeholders in a multidisciplinary project team dictates program success.

- Methodological rigor
- Steering committees
- Short protocol and (even shorter) CRF
- Fair market value fees to site
- Awareness of regulatory approval timelines
- Managing local affiliates (site selection and local KOL management)
- Adapting to reality (protocol amendments, rescheduling timeline)
- Remote monitoring

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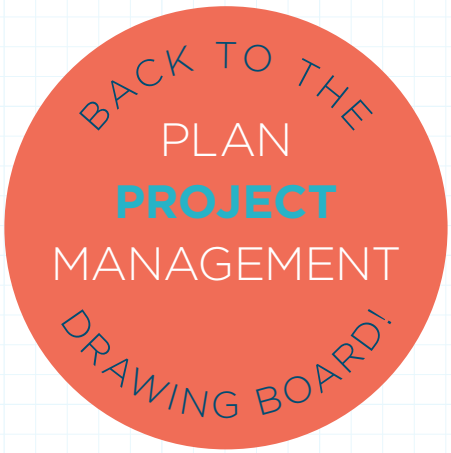
Planning for Disaster

Across indications and through time, registries provide unique examples of challenges for study implementation and completion. As in most programs reasons are multivariate. For example, if the mandate for the registry is based upon post-marketing commitments imposed by authorities, rather than generated by a sponsor for compelling medical or marketing objective, internal engagement mechanisms may be less robust. Frequently accompanied by urgency without regard to resources or timelines, these studies occasionally are hobbled by the lack of an adequate budget and -- counterintuitively -- are accompanied by insistence that phase 3 comprehensiveness and accuracy are expected.

The absence of a coordinating team in residence at the sponsor who can interface with a clinical research organization may jeopardize program completion, and the lack of internal late stage research experience mandates an antecedent phase of dialogue between a sponsor and CRO to set expectations appropriately.



- A Post-Marketing commitment imposed by Authorities
  - Must be done whatever it takes
  - URGENT!
- Not included in the development plan
  - Protocol from Hell: patient selection criteria
- No budget allocated
  - But phase III data quality expected
- No Team allocated
  - Contractor managing a CRO
- No interest to company staff
- No internal Late-Stage Research experience

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Rapprochement and a New Direction

Correspondingly, there has been an evolution in how observational studies in general, and registration studies in particular are approached. Initially marketing projects based upon needs for product positioning, these studies were heavily managed by local affiliates and local contract research organizations. Analyses and reporting were correspondingly measured. However, current observational studies including registries are characterized by good methodological rigor, defined hypotheses, validated measures, and thoroughly vetted methods of analysis and reporting. They are frequently managed by global medical affairs teams (GMA) working collaboratively with global CROs. Interestingly, communication with local affiliates has become even more critical to success requiring that affiliates receive regular updates on trial process. Partners in clinical research, local affiliates have access to sites during site training procedures, and participate in local investigator meetings using local languages and local CRAs.

Additionally, benefits occur bidirectionally between affiliates and CROs given the possibility of more informed site selection, assistance in managing those centers which have a checkered initiation, and facilitation of regulatory submissions. Global medical affairs at the sponsor likewise may then dedicate more time and resources to conceptual rather than operational demands for both interventional and observational studies correspondingly enhancing internal visibility.

Take Away Messages

Regardless of design and timing of observational studies, their importance in evidence generation can be subsumed in five axiomatic statements.

If it's after filing, it's probably late!

Strategic discussions which occur before pivotal registration trials are initiated are mandatory. *Frequently these discussions begin at the conclusion of phase 1 research, and for many companies engaged in portfolio evaluation these discussions occur even prior to IND enabling studies*, to assure that resources are available to generate data deemed critical by different stakeholders at the time of product registration.

Include patients in the deep end of the swimming pool!

During development, and prior to initiation of observational studies including registries, the systematic exclusion of patients with appreciable concomitant medication and comorbidities from registration trials will limit the ability to design subsequent studies which must include a representative cross-section of the population likely to ultimately receive therapy. *Although the proportion of the overall population evaluated may be small, these patients are likely those driving utilization within the indication, and thus become most informative.*

Capture outcomes, not just measures

Although the concept of a hierarchical approach to clinical outcomes is well-established, less certain is the outcome that would likely be most informative for a given stakeholder. *Therefore, a need to survey a range of providers and stakeholders for the purposes of exploring the value proposition of the product profile and the data necessary to support commercialization should occur prior to the design and the initiation of observational studies*. This includes the creation of registries which may have as one of their objectives the generation of data to inform the economic value of the intervention.

4 Think interaction effects

Once exiting a registration framework, interventional drugs, biologics, and devices enter into a complex matrix of clinical care which can include either pharmacotherapy or other supportive forms of therapy. These diverse interventions represent standards of care in the absence of a novel intervention. It is the interaction between established treatments with the newest "therapeutic neighbor" which creates a spectrum of unanswered questions in which augmentation or inhibition of therapeutic effects is possible. *As an illustrative example, would pharmacotherapy supporting cognitive remediation following traumatic brain injury facilitate or inhibit the impact of a systematic rehabilitation program in a clinical practice setting?*

5 Part of a publication package that begins with first in human studies

Observational studies, including registries, are within a portfolio of clinical trial designs yielding a variety of data used to inform decision processes for formulary placement, reimbursement, and provider and patient access to drugs, biologics, or devices. Methodologically rigorous, peer-reviewed publications contribute to health technology assessments and complement product labeling sanctioned by regulatory authorities. *These data explain treatment effects in terms that would resonate with a diverse audience, quantify the impact on a system of care, and otherwise facilitate decision-making by an increasingly diverse set of stakeholders – each with unique data demands impacting the overall clinical trial success.*

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