Optimizing Cost and Timeline Efficiencies in Late Phase Research

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Delineate Evidence Requirements

Evidence requirements to support the demonstration of safety, effectiveness, and value of a product now extend beyond market launch. Optimal product positioning and market uptake require a thoughtful multiyear, multidimensional strategy that culminates in an evidence base that will facilitate product coverage, reimbursement, and adoption. Value demonstration planning and strategic evidence gathering should ensure that available data are fully integrated and new research projects are designed to build on a unified body of evidence that will effectively communicate both the benefits and risks of a new medicine or technology. To achieve a comprehensive evidence base that meets the needs of a myriad of stakeholders, a broad array of scientifically robust national and international studies must be conceptualized, designed, and implemented within a relatively short period of time – typically no more than five to seven years. With research and development lifecycle costs of a single product estimated in the billions of dollars[1], evidence generation planning needs to be initiated as early as possible to ensure the right evidence is generated in the most cost-effective manner.[2]

Conceptualize Programs of Late Phase Studies Early

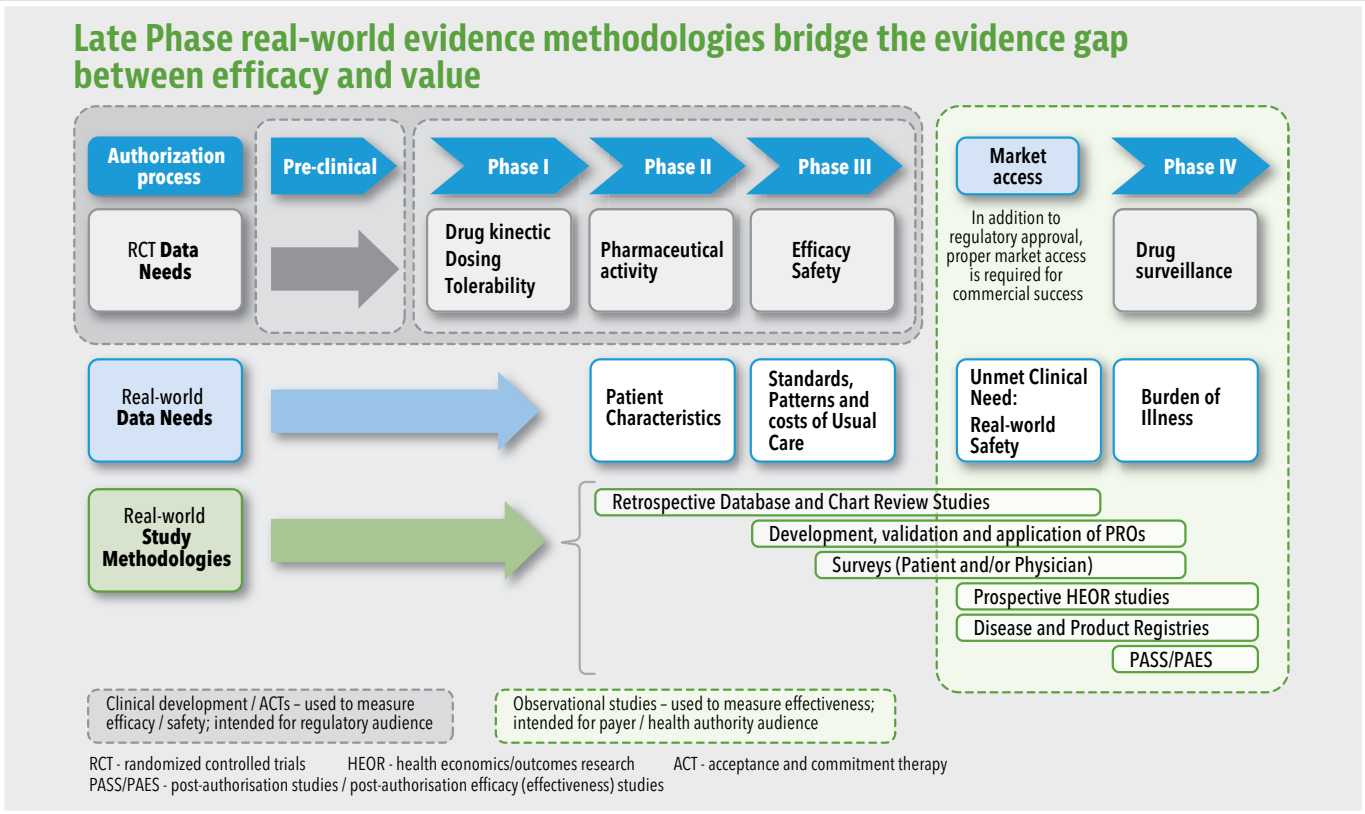
Fundamental to evidence generation planning and a real-world data strategy is a systematic evidence gap assessment and real-world data strategy. Once complete, methodologies for late phase evidence generation spanning analyses of secondary data sources, as well as de novo data collection needs, can be identified and prioritized – the latter associated with significant additional cost and timeline requirements. Even the simplest of protocol-driven, real-world data collection studies require significant time and investment, and costs increase further when compounded over multiple studies and years to support a full range of product safety, value, and effectiveness messages (see Figure 1).[3]

With the aim of optimizing cost and timeline efficiencies, multiyear research programs comprised of stepwise and synergistic de novo data collection studies should be conceptualized and executed. Unfortunately, given the sheer volume and diversity of data that are required to support multinational product launches, information silos, and organizational complexities within pharmaceutical and device companies, late phase studies are instead frequently designed and executed as separate stand-alone initiatives. These explanatory factors, as well as others, contribute from the outset to an inherent evidence gathering inefficiency that may require a paradigm shift in study planning if significant time and research dollars are to be saved.

Designs employed to gather real-world evidence vary markedly in terms of study parameters and scope, thus opportunities to incorporate efficiencies within a program of studies may not be immediately obvious. For example:

- Often considered retrospective registries, multi-national retrospective chart review studies can be used to build comprehensive patient-level repositories of international clinical and resource utilization data. These data can inform current patterns of treatment, including off-label prescribing, populate burden of illness, and other more traditional health economic evaluations, and inform trial or registry designs.

Figure 1. Real-world evidence (RWE) requirements span safety, effectiveness, and value



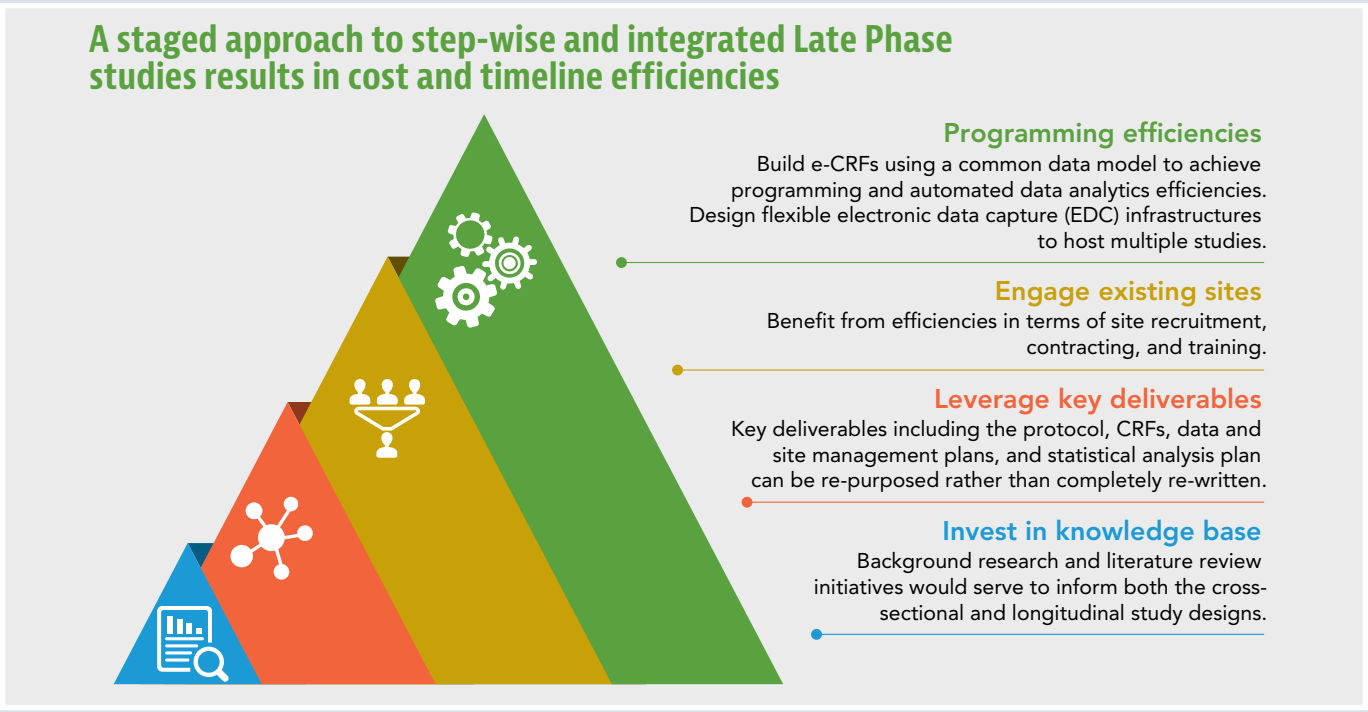
- Multifaceted prospective studies, including disease registries, are another important source of "benchmarking" data that also reflect natural history of disease and standards of care, but also include patient-reported outcomes (PROs) and other effectiveness outcomes. Pregnancy and product exposure registries are implemented to better understand real-world product safety and conditions of safe use.

- Pragmatic trials, which are observational in nature but with the added benefits of randomization, evaluate comparative effectiveness – increasingly important in the context of current trends in product commercialization and spending.[4]

Despite such differences in study aims, objectives, and specifications, important cost and timeline efficiencies can be realized by systematically seeking out and building upon methodological and operational synergies. Each of these study types aim to collect real-world patterns of care, and clinical, safety, and effectiveness outcomes. Because each of these studies would be executed as part of the same product's commercialization process, key design elements – including patient selection criteria, sub-groups of interest, clinical and patterns of care variables of interest, and other patient outcomes – are likely to overlap significantly. For example, though research questions may vary markedly, patient selection criteria, subgroups of interest, clinical and resource use variables, and other outcomes of interest are likely to be consistent. These synergies can be exploited both by "recycling" selected content from study documents, such as protocols, case report forms (CRFs), informed consent forms, statistical analysis plans, and even statistical programming code. If the number of study protocols can be reduced, so can the number of site contracts and ethics and other mandatory approvals, as well as the number of months of study start-up. While the efficient use and repurposing of study materials from one project to another over time is primarily a documentation, communication, and knowledge transfer exercise, combining study protocols to achieve hybrid, longitudinal designs requires a bold, strategic vision and multiyear commitment of resources. Those willing to make this level of upfront strategic investment do so with an inherent belief that over the product commercialization period, the total cost and resource requirements of the program as a whole will be significantly less than if each study was conducted as a standalone initiative (see Figure 2).

A schematic representation of a stepwise approach to the integration of multiple real-world studies, including a chart review, a prospective study, and a product registry over multiple years, is shown in Figure 3. Foundational chart review activities provide important information about variability in patterns of care and clinical outcomes, but they can also serve as the means to identify

Figure 2. Opportunities for synergies and efficiencies



prevalent cases of interest for enrollment in a prospective study such as a disease registry. Once implemented, prospective studies including disease registries, within which a wealth of clinical, health economic, and PRO endpoints can be collected, can also be a highly efficient framework to evaluate the real-world safety profiles of new and emerging products once they enter the usual care environment.

Leverage Investigator and Patient Networks

Study start-up activities, including site recruitment, contracting, regulatory document collection, and training, are key drivers of total study cost regardless of the type of study executed. Therefore, strategies such as the early identification and implementation of a network of investigators who agree to a mandate to support a program of synergistic studies over time will result in measurable cost and timeline efficiencies. Once enrolled in a research network, pre-screened investigators amenable to participation in multiple studies and sub-studies will contribute to decreased start-up time and burden from one study to the next. While randomized controlled trials (RCTs) typically require the involvement of academic or specialty care centers, observational studies generally draw upon the same mix of study sites that better reflect routine medical care. It is postulated that this approach would ensure broad unselected populations, avoid competition between RCTs and registries, and stimulate and encourage scientific and clinical input from academia.

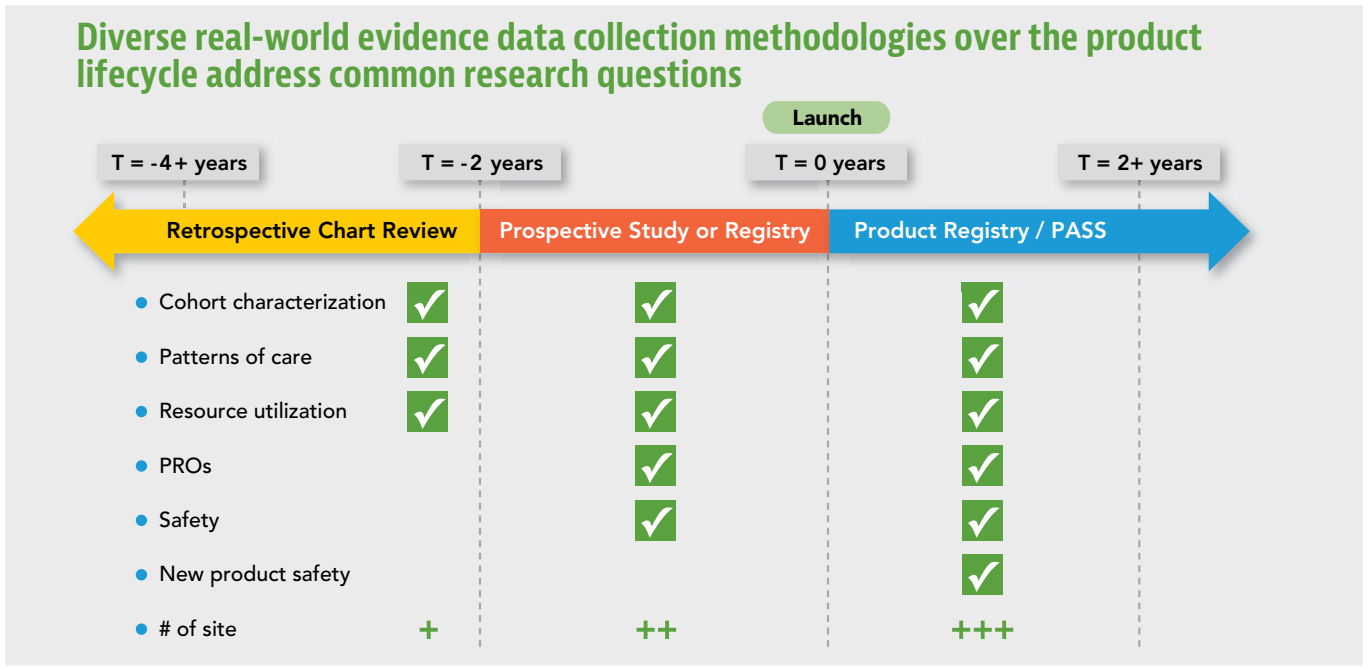
Reliance upon pre-existing networks of patients is also an appealing strategy for recruitment and enrollment. Electronic medical record (EMR) or other health data, including diagnostic and pharmacotherapy information, can be analyzed to identify potentially eligible patients, or alternatively, populations of patients can be built expressly for the purpose of study participation. Additionally, numerous online, high volume, international panels of pre-consented and screened populations of patients have been established that can support scientifically rigorous international burden of illness assessments.[5] Popular patient support and advocacy organizations can also be utilized to access specific patient cohorts of interest.[6]

Prioritize Innovation and Technology

Traditional approaches to real-world data analytics are constrained by available programming resources and, typically, require custom programming for each analysis. Moreover, format and programming differences across study datasets make it inefficient to execute and difficult to meaningfully compare outcomes.[7] These challenges may be resolved through standardization – in particular, through the use of a common data model (CDM), such as that developed by the Observational Medical Outcomes Partnership (OMOP)[8] and currently maintained and used for research by the Observational Health Data Sciences and Informatics (OHDSI) collaborative.[9]

Using a CDM to develop study CRFs and standardized data formats allow for the pooling of data from de novo data collection studies as well as data from secondary

Figure 3. Stepwise approach to the integration of multiple real-world studies



administrative claims or EMR sources resulting in tailored repositories of patient-level data. A CDM approach to evidence generation also allows for the use of technology-enabled automated data analytics platforms, such as Evalytica[10], which permit "faster time to data." Data insights sooner can support strategic and timely data dissemination and reporting, as well as to inform the design of subsequent downstream studies – or even result in the adaptation of a current study design through an amendment prior to close-out.

Designing and implementing an optimal electronic data capture and communications infrastructure early in the product commercialization process can also result in significant efficiencies. Innovative, multimodal EDC systems far exceed basic data capture capabilities in terms of core functionality. A tailored, fit for purpose EDC system can serve as an epicenter of research activity, facilitating study recruitment and enrollment, data capture and management, and global study communications. Study Coordinating Centers can use such systems to manage multiple studies across multiple study sites simultaneously, as well as to enhance study and data quality in real time. Investigators can access these infrastructures to enter study data, download study reports and their own data reflecting their patients' clinical and study outcomes, and learn about new studies opening for enrollment.

Synergies and efficiencies across a program of studies resulting from early investment in an EDC infrastructure can be realized, particularly in relation to common core data elements. There will be significant overlap in key variables such as patterns of care, resource utilization, and clinical outcomes of interest. By creating libraries of e-CRF common data model formats, data dictionaries, statistical analysis plans and associated programming code and validation rules, and drawing upon these investments from one study to the next, research time and costs can be greatly reduced. This approach will also result in consistency across study datasets which will permit the pooling and cross-analysis of standardized data from multiple studies, especially important in the context of increasing comparative effectiveness evidence requirements.

Increase Your Return on Evidence Gathering Investments

Late phase strategic and synergistic real-world evidence gathering across the product lifecycle can and will contribute significantly to cost and timeline efficiencies. To this end, the following general recommendations may be useful.

- Engage in early and rigorous value development planning including the delineation of a tailored real-world data strategy. A plan which clearly delineates the "right" real-world data for the "right" audience at the "right" time will ensure that data collection efforts are focused and coordinated and contribute to successful reimbursement and market access outcomes.
- Design studies in stepwise and strategic fashion, and strive to combine designs and research objectives into

a reduced number of study protocols where possible. The integration of multinational chart review studies and disease and product registries are particularly well-suited to this synergistic approach.

- Build CRFs and underlying data structures using a common data model to permit advanced and automated data analytics across various pooled data sources.
- Establish a central repository of study documents and materials including protocols, e-CRFs, statistical analysis plans, CDM data formats, and coding to ensure optimal use and re-use of fixed cost investments.
- Implement an EDC infrastructure early in the product lifecycle to support a standardized approach to the collection of key data elements, investigator communications, and recruitment within and across studies.
- Build a network of investigators who are committed to a well-described, scientifically rigorous, multi-year program of complementary studies.
- Initiate network study sites with a mandatory core study protocol designed to achieve a standardized, longitudinal core minimum dataset. Offer subsequent opportunities for new and existing sites to "opt in" to additional studies and sub-studies of interest through notifications communicated via the EDC infrastructure.
- Offer participating investigators opportunities to access their own data electronically in real time. Benchmarking patient data within and across study sites through the use of customized reports and data visualization techniques can serve as an effective participation incentive by offering investigators important clinical information as well as opportunities to participate directly in study publications.

An early adoption and implementation of strategic study designs, operational infrastructures, and technology-enabled data analytics can provide important opportunities for significant savings in terms of commercialization timelines, costs, and human resource requirements. Though this approach does demand a greater investment earlier in the product lifecycle in relation to the planning and execution of real-world studies, the return is likely to exceed expectations. As research dollars decrease and evidence requirements increase, new and sustainable research strategies and methodologies that contribute to a high quality, on-time delivery of an evidence base that meets market access stakeholder requirements are clearly warranted.

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