NEWDIGS

LEAPS

Learning Ecosystems Accelerator for
Patient-centered, Sustainable innovation

RESEARCH BRIEF

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Transforming Real-World Evidence in Biomedical Innovation: Advancing the Design of Collaborative Disease-Focused Learning Ecosystems.

The LEAPS methodology begins by answering two structured questions – WHAT evidence to produce, and HOW to produce it, as outlined in this two-part Research Brief series:

- Part I: Baking the Cake: A Decision-Driven Framework to Planning Fit-for-purpose Evidence Across Stakeholders (WHAT)[1]
- Part II: Evidence-Generation Platforms: Enhancing the Efficiency & Scale of Evidence Production (HOW)

INTRODUCTION

The MIT NEWDIGS "LEAPS Project" is *transforming how we plan, produce, and use real-world evidence* (RWE) for therapeutic products to systematically improve patient outcomes. The NEWDIGS 3-Layer Cake framework, described in Part I of this two-part Research Brief series, guides a multi-stakeholder process for planning evidence that is fit-for-purpose for key decisions each stakeholder makes related to the development, access, and use of biomedical innovations.[1] This Research Brief focuses on how we enhance the 3-Layer Cake by adding a 4th layer to support system-design opportunities that drive efficiency and scale in evidence generation.

THE CHALLENGE

Successfully delivering on the *promise of biomedical innovation* in the world of value-based healthcare requires targeted clinical decision-making, where patients are provided the right treatment at the right time for their needs. However, barriers to achieving this goal include important knowledge gaps, along with challenges to addressing these gaps. Specifically, the current approach to biomedical evidence generation is expensive, inefficient, fragmented, and narrowly focused, i.e. "one question, one drug, one stakeholder."

KEY TAKEAWAYS

Value-based healthcare requires real-world evidence (RWE) to inform treatment choices for patients to maximize the likelihood of providing the right treatment at the right time.

Meeting these major, complex evidence needs will require modernizing RWE generation to enhance efficiency, scale, and utility for all stakeholders.

Core to this evolutionary advancement will be the application of platform strategies to the production of RWE.

Adding the 4th layer to the 3-Layer Cake framework provides a structure to support the multi-stakeholder collaborative design of RWE platforms that will be critical for improving decisions and outcomes in a disease-focused learning ecosystem.

The LEAPS pilot for rheumatoid arthritis (RA) in Massachusetts (MA) – the "RA MA pilot" – will evaluate this approach optimizing therapeutic regimens in a real-world setting, and will inform generalizable insights into the design and use of RWE generation platforms for perpetual learning.

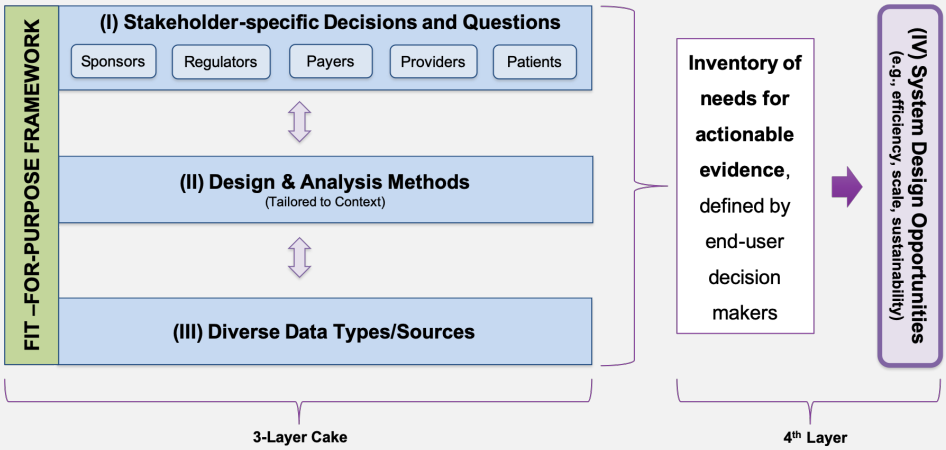

Figure 1. **LEAPS "4-Layer Cake" Supports the Development of a Real-World Evidence Plan that is Fit-for-purpose for Key Decision Makers.** Layers I-III guide biomedical evidence planning to ensure the evidence generated answers the right questions and is regarded as actionable by each stakeholder. Layer IV supports the design of platforms that can address evidence needed by multiple stakeholders, in ways that are more efficient, scalable, and sustainable.

Filling critical knowledge gaps to improve therapeutic regimens, including treatment combinations and sequences, requires both (1) actionable evidence that appropriately informs the decisions of all stakeholders, and (2) the ability to produce the evidence in ways that are time and cost efficient.

Actionable Evidence (WHAT)

The NEWDIGS 3-Layer Cake, introduced in Part I of this Research Brief series, enables actionable evidence generation through a strategic framework that identifies the evidence needs and requirements for stakeholder decisions.[1]

The 3-Layer Cake was originally developed for lifecycle-based evidence planning for a single therapeutic product in the NEWDIGS Adaptive Licensing Project.[2] The LEAPS Project, however, recognizes a critical shift from product-centered to disease-focused learning. This shift is beginning to happen within the therapeutic area groups of some large biopharmaceutical companies. While these efforts are enabled by greater access to large, diverse data sets across the healthcare system, they remain costly, and the value captured from them is narrowly focused on the proprietary needs of the company. While some efforts must remain proprietary, there are likely to be opportunities for collaboration rather than duplication of efforts, reducing waste and inefficiency for the system. A central question in LEAPS is when, and how, are stakeholders able to drive greater value by working on disease-focused learning together rather than alone, beginning with activities centered around RWE generation.

Efficiency and Scale (HOW)

The 4th layer of the 3-Layer Cake (Figure 1) specifically empowers us to address this shift to disease focused-learning and systematically identify multi-stakeholder collaboration opportunities for greater efficiency, scale, and impact in patient-centered decisions and outcomes. This collaboration will not replace complementary activities in evidence generation but can leverage economies of scale (cost advantages that come with increased production efficiency) and cost-sharing among multiple stakeholders, to the benefit of all stakeholders, especially patients. System-design opportunities offer the potential for sustainable, perpetual learning that provides actionable evidence for multiple stakeholders through one evidence stream.

The LEAPS project drives value in two dimensions: therapeutics and knowledge. As such, application of the 4-Layer Cake framework serves two goals:

1. **Therapeutic:** Exploit the potential value of medicines by improved targeting of their use to the right patient at the right time.
2. **Knowledge:** Enhance our ability to produce evidence (needed for Dimension #1) at scale, with greater time and cost efficiencies.

PLATFORM STRATEGIES FOR BIOMEDICAL INNOVATION

Meeting these complex RWE needs requires the application of platform strategies to drive efficiency and scale of evidence generation. A platform is generally defined as a foundation (physical or virtual) that connects different people or groups either for a common purpose or to share a common resource.[3] While a *product platform* works within an organization or supply chain, an *industry platform* works both in and outside an organization, i.e., within "the ecosystem," thus enabling transactions and innovations that might not otherwise occur. Platform strategies have driven the advancement of the high-tech industry (e.g., Apple, Google, Facebook)[4] but have only recently been explored for evidence production in healthcare, originating in oncology with adaptive platform trials of investigational drugs to advance precision medicine.[5]

Pre-market platform strategies in biomedical innovation

Platform trials are adaptive, multi-arm designs that continuously evaluate multiple treatments in the context of a single disease, both in parallel and sequentially over time.

Platform trials offer operational efficiencies by way of an established infrastructure, a master investigational new drug application (IND), a master protocol, centralized and standardized components (e.g., central institutional review board, standardized informed consent form, standardized data collection, standard comparator arm), and economies of scale. Novel design elements enable sample-size efficiencies via adaptive randomization, reducing the research burden and potential risk to patient participants, and ongoing evaluation of patient outcomes to inform changes as the data accumulates. As such, unsuccessful therapies can be discontinued while successful therapies can be advanced more quickly, and the patient population in which a drug will be most successful is efficiently identified, reducing risk and uncertainty for all stakeholders.

Post-market platform strategies in biomedical innovation

Adaptive platform trials have since expanded to disease areas beyond oncology, and more recently to real-world settings where key elements of adaptive platform trials are embedded into clinical practice.[6,7] Using rheumatoid arthritis (RA) as a model for a Massachusetts (MA) based pilot, the "RA MA pilot," **LEAPS is harnessing lessons learned from these pioneering endeavors to target the next frontier in biomedical evidence-generation platforms: applying platform strategies to the real-world treatment of chronic diseases in ambulatory settings.**

Platform strategies for real-world data in biomedical innovation

While real-world data (e.g., electronic health record (EHR), administrative claims, socioeconomic) are commonly utilized for post-market biomedical research, this research is most often carried out in a single, large, centralized data source, which limits its utility. Advancements in technology and analytic methods have made it possible to apply platform strategies to distributed real-world data sources offering the potential for greater scale, efficiency, and utility, while also maintaining data privacy. LEAPS will explore new ways to apply these capabilities to RWE generation.

LEAPS: INFORMING DESIGNS FOR PLATFORM STRATEGIES.

The RA MA pilot provides a testbed opportunity for the collaborative design and demonstration of multiple coordinated platforms that are scalable, sustainable, and interoperable. The 4-Layer Cake supports this endeavor by providing structure to systematically identify **what** evidence is needed (layers I-III) and **how** to generate it (layer IV).

Currently, two potential platform designs that target regimen optimization in RA are being explored in ongoing multi-stakeholder Design Labs: the Real-World Discovery Platform (RWDP) and the Adaptive Point of Care (APoC) platform. These two initial platform designs are coordinated in the overall goal of improving regimen optimization in RA and are tailored to the particular question each is designed to address (Table 1). *LEAPS leverages the fact that, while different stakeholders make different decisions in the system, there are some shared needs for specific elements of evidence.* For example, in the RA MA pilot, identifying clinically meaningful subpopulations of patients with RA could improve decision-making for all stakeholders.

Real-World Discovery Platform (RWDP)

Identifying clinically meaningful subpopulations is a key goal of a RWDP design. A RWDP will harness real-world data from diverse data sources (e.g., EHR, administrative claims, socioeconomic, patient-generated) to identify demographic, clinical, molecular, and/or radiomic (abstraction of data from medical images such as magnetic resonance imaging (MRI)) characteristics that are associated with drug effectiveness; predictors might then better direct patients to the best therapy for their needs. A RWDP design allows for an iterative process of perpetual discovery and refinement of potential predictive markers, whereby characteristics in one

4-Layer Cake Level	Real-World Discovery Platform (RWDP)	Adaptive Point of Care (APoC) Platform
I. Common evidence needs that address multiple **stakeholder-specific decisions**	Clinically meaningful subpopulations	Multi-factorial comparative effectiveness
II. **Design & Analysis Methods**	Open algorithm across diverse distributed data sets; Artificial Intelligence/Machine Learning	Adaptive randomization; embedded at point-of-care
III. **Diverse Data Types/Sources** (flexible staging, sequencing, scaling)	Retrospective data: EHRs, claims, registries, etc.	Prospective data: EHRs; potential to enrich with links to other data sources (e.g., patient registries)
IV. **System Design Opportunities**	Address the needs of multiple stakeholders; economies of scale; cost-sharing; adaptive system with the potential for sustainable, perpetual learning	

Table 1. **Application of 4-Layer Cake to Design of Potential Platforms for the RA MA Pilot.**

data source can be substantiated and refined in another data source.

The RWDP design (Table 1) builds on important foundational work in real-world data in general, e.g., Informatics for Integrating Biology and the Bedside (i2b2) project,[8, 9] and RA in particular,[10, 11] to employ platform strategies that offer the potential to scale across many types of similar data types, as well as to link across diverse data types. It is envisioned as a federated system, in which open source algorithms and models are developed centrally, and then distributed across a network for use and refinement. The collective intelligence from insights generated from network users can then be harnessed to improve the central algorithms and models and can be shared with the data owners. This approach exploits the value of "big data" without the costs and risks of patient-level data sharing. That is, the algorithm "travels" to the data, rather than LEAPS creating a shared data pool in a centralized repository.

A RWDP will apply current artificial intelligence and machine learning techniques to this diverse, distributed set of data sources to identify and replicate predictive markers. The greater scale and diversity of data types are expected to improve the success rate for discovering predictive markers while also reducing waste and inefficiency.

Adaptive Point of Care (APoC) Platform

An APoC platform (Table 1) is designed to produce multifactorial comparative effectiveness evidence to inform treatment selection, including combinations and sequences of therapeutics, in a real-world setting. An APoC platform will be embedded into decision-making at the point of care and will employ adaptive methods to continuously learn and improve treatment selection for a given patient profile. This design incorporates elements from Adaptive Platform Trials, such as adaptive randomization and a master protocol, but also ensures that key criteria for embedded point of care studies such as clinical equipoise, EHR compliant workflows, and minimal disruption to clinical care are implemented.

CONCLUSION

The landscape of healthcare and biomedical innovation is rapidly evolving. We need to modernize how we plan, produce, and use RWE to ensure that value-based healthcare and biomedical innovation are both successful and sustainable. This change will require multi-stakeholder collaboration to apply platform strategies that advance the evolution of disease-focused learning ecosystems. The RA MA pilot provides a testbed opportunity to design and evaluate the application of these strategies to the production of RWE to advance regimen optimization. The 4-Layer Cake will be instrumental in supporting the collaborative design of multiple RWE platforms for the pilot. More broadly, the LEAPS project will help build the capability for efficient, actionable, RWE generation to advance regimen optimization, and will fuel insights into where collaborative disease-focused research is a feasible and appropriate complement to other RWE generation efforts.

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ABOUT LEAPS

The LEAPS Project (Learning Ecosystems Accelerator for Patient-centered, Sustainable innovation) is advancing the mission of the MIT NEWDIGS consortium—*to deliver more value from biomedical innovation faster to patients, in ways that work for all stakeholders*—through a new collaborative systems approach to the planning, generation, and use of evidence across R&D and healthcare delivery. A model system for Rheumatoid Arthritis will be piloted in Massachusetts (2020 launch), and will inform related efforts in other diseases and geographies. Success in LEAPS targets better patient outcomes while also reducing waste and inefficiency across the system.

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