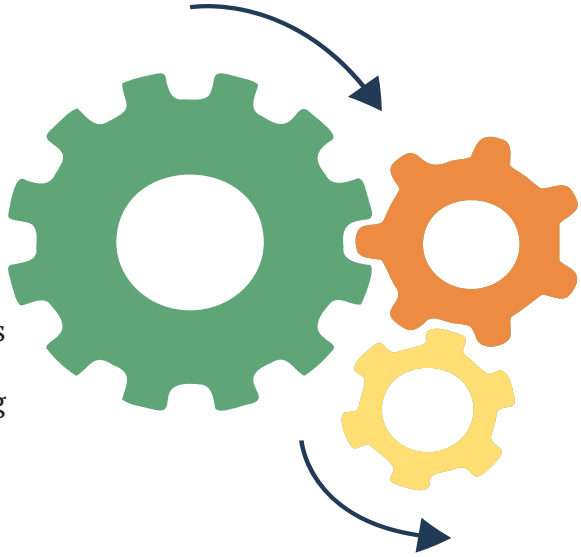
Medicines Development Modernization Initiative

Roadmap and Strategy

April 2021

MDMi
Medicines Development
Modernization Initiative



Medicines development is a lengthy, complex, and costly process, imbued with a high degree of uncertainty that a drug candidate will actually succeed and reach the market. Rapid scientific advances are enabling a greater understanding of diseases at the molecular level; but at the same time, increasing clinical trial complexity and economic pressures have made the medicines development process more difficult. On average, from start to finish, the clinical development phase takes six to seven years, and the average cost to research and develop each successful medicine is estimated to be $2.9 billion, including the cost of the thousands of compounds that may fail at some point throughout the R&D process.[1] Over the past decade, the return on investment in pharmaceutical R&D has fallen from more than 10% to just 1.8%,[2] forcing a reallocation of assets away from larger population chronic diseases and antimicrobials, and toward medicines that treat increasingly narrow populations.

Novel medicine development tools (MDTs), such as real-world evidence (RWE), Bayesian statistical methods, seamless and adaptive trial designs, and emerging digital technologies,[3] can unlock systemic changes in medicines development and reverse these trends. Although their use has been legislatively or regulatorily recognized, these MDTs have not been widely integrated into drug development programs and the clinical trial process, and therefore considerable opportunity exists to further modernize medicines development and drive greater efficiency into the process. In particular, the combined use of multiple DDTs within medicines development programs across different therapeutic categories has a largely untapped potential. The effective integration of MDTs into medicines development is a public health imperative. Approximately 133 million Americans—45% of the total population—are living with at least one chronic disease,[4] and 7 out of 10 deaths in the U.S. are due to chronic disease.[5] The integration of MDTs in an ecosystem that recognizes and supports the public health benefits of innovation will dramatically reduce the time and cost of medicines development and allow continued innovation across all disease and population categories, both rare and prevalent, short-term and chronic.

The roadmap outlined in this document provides a comprehensive strategy to integrate MDTs and stakeholders in the medicines development ecosystem to ensure continued access to important medicines for all patients.

---

[1] DiMasi JA, Grabowski HG, Hansen RA. Innovation in the pharmaceutical industry: new estimates of R&D costs. Journal of Health Economics 2016;47:20-33.

[2] Deloitte, *Measuring the Return from Pharmaceutical Innovation* (2019), available at: https://www2.deloitte.com/us/en/pages/life-sciences-and-health-care/articles/measuring-return-from-pharmaceutical-innovation.html#:~:text=R%26D%20returns%20have%20declined%20to,2018%20to%20%241%2C981%20in%202019.

[3] This Roadmap is intended to capture and consider MDTs as broadly as possible, including both actual measurable markers and end-points as well as strategic/tactical approaches such as continuous development. Other MDTs include model-informed drug development, biomarkers, and patient-focused drug development. In the U.S. regulatory environment, these are commonly referred to as "Drug Development Tools." We have adopted the more global phrase "medicine development tools."

[4] https://www.fightchronicdisease.org/sites/default/files/docs/GrowingCrisisofChronicDiseaseintheUSfactsheet_81009.pdf

[5] Ibid.

Roadmap to Transform the Medicines Development Ecosystem

The looming public health crisis associated with the suboptimal medicines development ecosystem is being driven by two major factors: the length of time and the cost of the medicines development process. In light of the finite resources available for medicines development, both factors significantly limit the number of medicines that can be developed and consequently the diseases and patients that can be treated. An unintended consequence is to drive research and development to those dire and uncommon diseases for which the regulatory environment has established facilitated or rapid reviews that make recouping of cost more likely. This is resulting in a daunting void in drug development for more common chronic diseases, infectious diseases, and more complex diseases. Addressing these factors is an imperative for the medicines development ecosystem and public health.

To achieve the objectives of reducing time and cost of medicines development, it is critical to identify, understand, and categorize the systemic drivers[6] of those two factors and the strategies that can be deployed to address those drivers. For example, certain diseases such as obesity involve numerous environmental and cultural factors that have driven reliance on data generated in a clinical trial setting, including increasingly diverse and very large clinical trial populations. This has created greater difficulty recruiting trial participants, expanded the need for more expensive infrastructure, and dramatically increased the amount—without increasing the variety or value—of data gathered and managed from clinical trials. Fortunately, modern MDTs, such as real-world evidence and digitally enabled decentralized clinical trials, hold the potential to overcome those challenges if fully integrated into the clinical trial design and the regulatory approval process. Achieving the integration of facilitating MDTs—and integration by inclusion of the stakeholders required for successful implementation—is the central purpose of the Medicines Development Modernization Initiative (the Initiative).

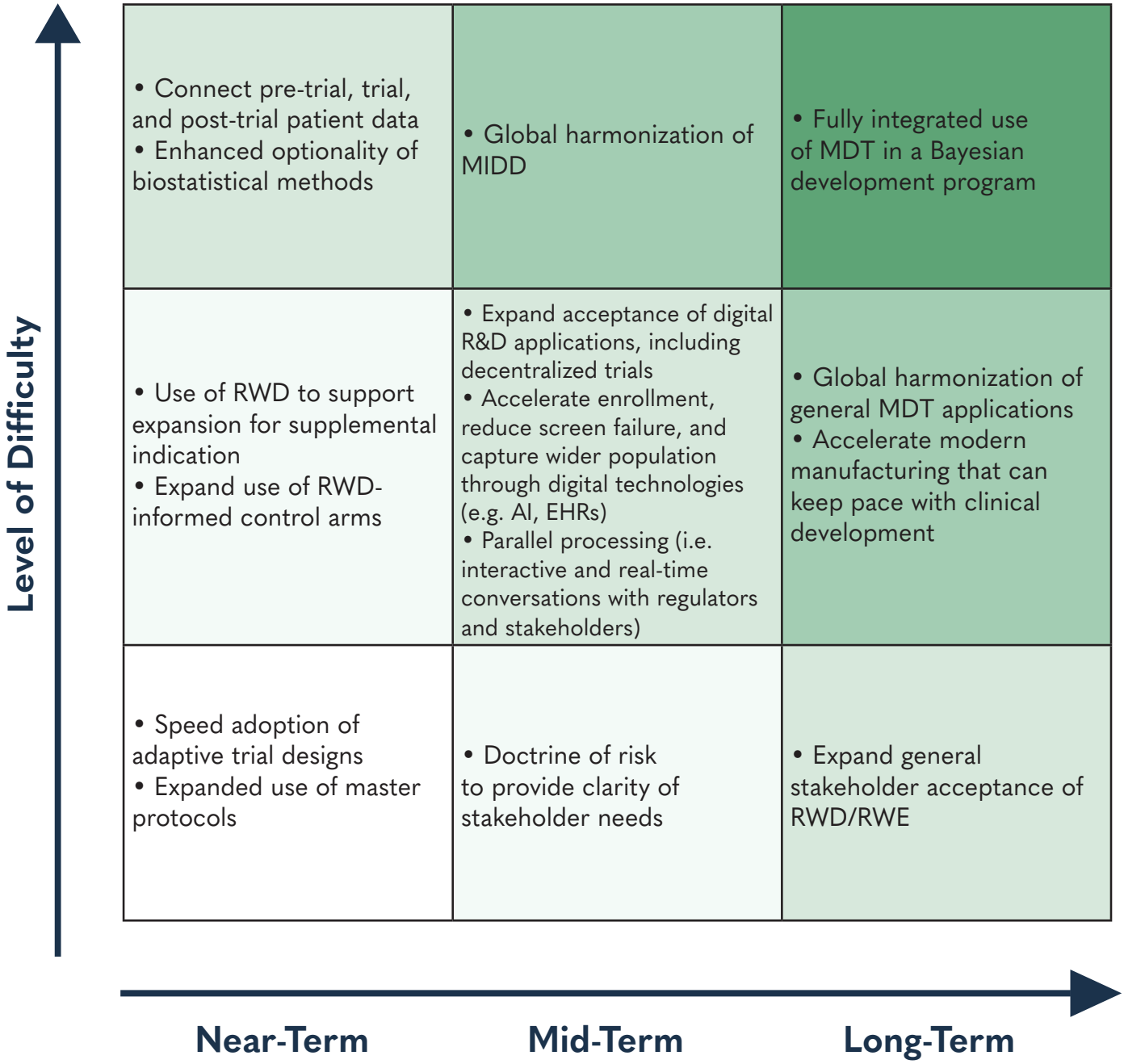
Understanding the Drivers of Time and Cost

To understand precisely where and how integration of MDTs and the role of stakeholders fit into achieving the objective of reducing time and cost, it is important to first understand the systemic drivers of time and cost and the strategies that can be deployed to address those drivers. The following chart identifies those drivers and strategies as defined by the prior work of this Initiative.

[6] A number of ongoing stakeholder initiatives are focused on identifying and addressing the operational and process-related drivers of the time and cost of medicines development. This initiative, however, is focused on systemic transformation to attain significant reductions in the time and cost of medicines development. While those other initiatives may provide insightful learnings that can be leveraged to achieve systemic transformation, these efforts are complementary in achieving those goals.

Drivers of Time and Cost	Strategies and Initiatives to Address Drivers
Desire for Absolute Certainty	
Large trial sizes (in certain product categories)	• Advance global harmonization of MIDD • Reduce difficulty of trial recruitment and enrollment through decentralized trialsdigital technologies • Expanded use of biomarkers for patient stratification
Demand for data collected in a clinical setting	• Expand acceptance of decentralized trials • Expand stakeholder acceptance of RWD/RWE
Reliance on traditional control arms	• Expand use of master protocols • Advance RWD-informed control arms • Advance global harmonization of MIDD
Misalignment of Stakeholders	
Lack of up-front understanding of stakeholder needs	Develop and advance a Doctrine of Risk to add transparency to stakeholder needs
Failure Rates	
High rate of failures	• Expand use and acceptance of MIDD • Expand use and acceptance of digital R&D applications • Expand use and acceptance of adaptive trial designs • Expand availability of validated and clinically relevant surrogate end point biomarkers
Hesitancy to end development programs	Expand use and acceptance of MIDD
Regulatory Complexity	
Large trial sizes (in certain product categories)	• Advance global harmonization of MIDD • Reduce difficulty of trial recruitment and enrollment through decentralized trialsdigital technologies • Expanded use of biomarkers for patient stratification
Dead time between trials	Enhance optionality of biostatistical methods
Variability of global requirements	• Advance global harmonization of MIDD • Advance global harmonization of other MDT acceptance
Difficulty of adjusting trial design midstream	Speed adoption of complex innovative trial designs
Excessive ALCOA data requirements	Expand stakeholder acceptance of RWD/RWE
Outdated Systems and Processes	
Expectation to produce certain types of data even when not the best types of data	• Expand stakeholder acceptance of RWD/RWE • Drive acceptance of RWD to support supplemental indications • Expand stakeholder acceptance of digital R&D applications
Difficulty compiling and sharing comprehensive data	• Enable connection and continuous flow of pre-trial, trial, and post-trial patient data • Implement strategies for trial data management and movement
Reliance on traditional control arms	• Expand use of master protocols • Advance RWD-informed control arms • Advance global harmonization of MIDD

These strategies and initiatives to integrate MDTs are the key to addressing time and cost and improving success rates. Prioritization of those strategies and initiatives to help inform this roadmap is conceptualized in the following matrix.



Envisioning an Integrated Medicines Development Ecosystem

A medicines development ecosystem that addresses patients' needs faster and at lower cost requires both the integration of MDTs and the integration of stakeholders. Today's medicines development process is too often locked into a 50-year-old, inefficient, incomplete model that has progressively added unnecessary time and cost throughout the ecosystem and has failed to acknowledge or incorporate the many scientific advances that have occurred in this timeframe. Stakeholder needs and expectations are too often incomplete, compartmentalized, unsought, or lacking in upfront transparency. Tremendous energy and resources are

expended to develop a medicine and march through the long, linear, step-wise requisite process in hopes it meets those unclear stakeholder needs and expectations. And too often, the end result of this long, costly process is misaligned with stakeholder and/or patient needs.

The long-term goal of the Initiative and this Roadmap is to create a modern approach that brings all stakeholders and the technological and scientific advances of recent decades fully to bear. Much like the technology industry's transition to agile, user-facing software development, this modern medicines development ecosystem will include a transparent process to collect comprehensive, detailed needs and expectations from all stakeholders up front, routine interim opportunities to gather stakeholder feedback as the process progresses, and the ability to transparently shift direction as interim feedback is collected—all with the goal of more rapidly and efficiently delivering medicines that are more valuable to more stakeholders.

This more integrated, streamlined ecosystem will facilitate the use and integration of MDTs, both in clinical trials and programmatically, and unlock the potential of those MDTs. Normalizing MDTs throughout the ecosystem will create a full toolkit of MDTs that can be applied in combinations tailored to specific medicines and diseases in order to deliver medicines that meet public health needs faster.

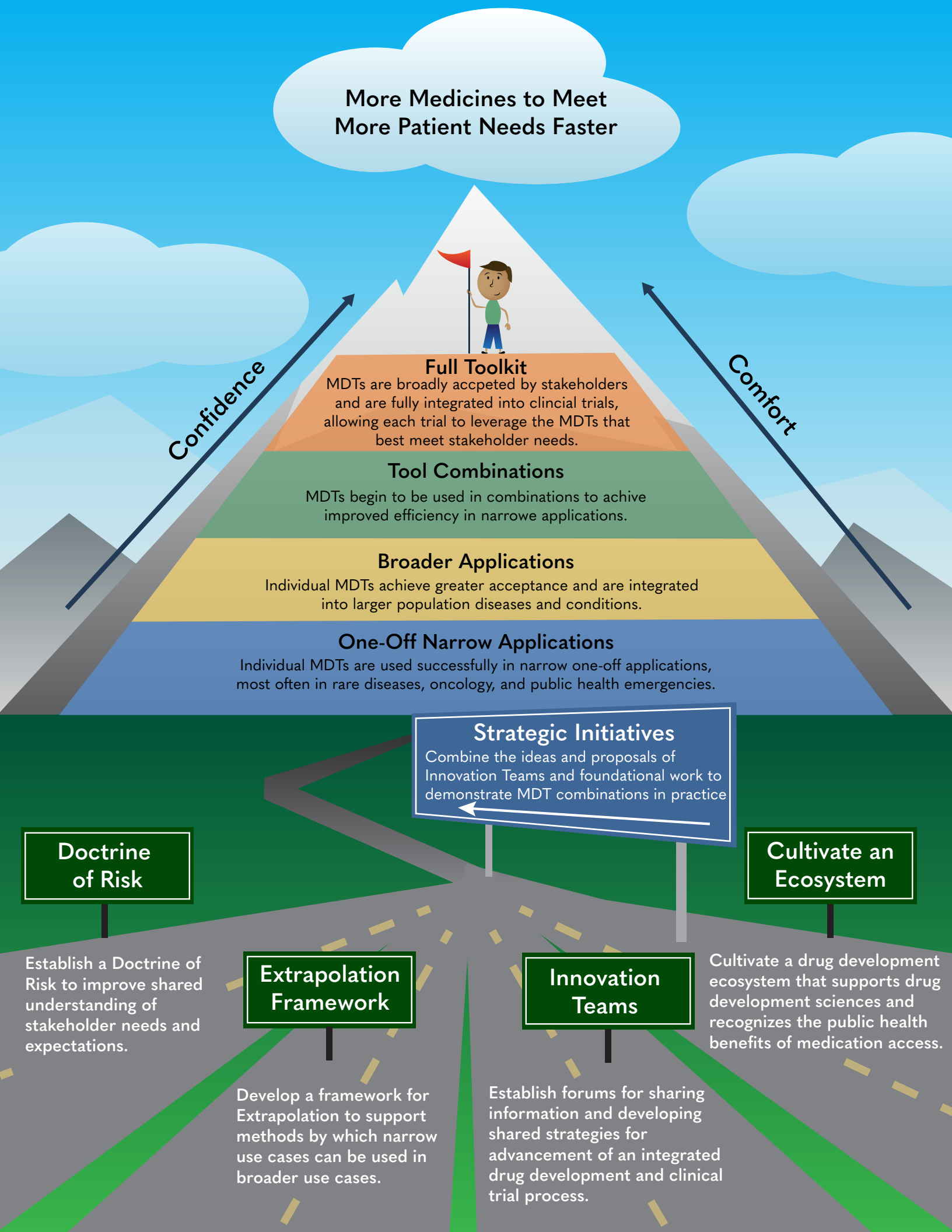
A Strategy for Integrating MDTs and Stakeholders

The integration strategy includes three core components, outlined in the graphic below.

1. A **defined vision** for the iterative expansion of MDT use and the combination of ways in which MDTs can be used collectively in an integrated ecosystem.
2. **Strategic Initiatives** of the Steering Group to accelerate the integration process.
3. Four **core strategies** to support the development of those Strategic Initiatives.

Interative Expansion of Medicines Development Tool (MDT) Acceptance

Acceptance of an MDT is a slow and difficult process. The use and regulatory acceptance of an MDT requires changes in established, deeply engrained systems and processes, and the inertia of those existing processes is difficult to overcome. The risks associated with use of MDTs often create a vicious cycle in which biopharmaceutical companies are hesitant to use MDTs outside of narrowly defined, lower-risk scenarios because the investment is too significant to risk without certainty that other stakeholders—most importantly regulators, patients, and payers—will accept the results of trials that leverage those MDTs. Conversely, those other stakeholders are unable to build the experience necessary to understand and become comfortable with the results without broader use. This futile cycle creates a slow, sporadic trajectory in which a limited number of the available MDTs are first conceptualized, then gain narrow acceptance—often in pilot contexts, in rare diseases, or in medicines targeting narrow patient populations—and then slowly gain broader acceptance. As the numerous efforts to advance RWE have demonstrated in recent years, this iterative process can be slow and difficult.


More Medicines to Meet
More Patient Needs Faster
Confidence
Comfort
Full Toolkit
MDTs are broadly accpeted by stakeholders and are fully integrated into clincial trials, allowing each trial to leverage the MDTs that best meet stakeholder needs.
Tool Combinations
MDTs begin to be used in combinations to achive improved efficiency in narrowe applications.
Broader Applications
Individual MDTs achieve greater acceptance and are integrated into larger population diseases and conditions.
One-Off Narrow Applications
Individual MDTs are used successfully in narrow one-off applications, most often in rare diseases, oncology, and public health emergencies.
Strategic Initiatives
Combine the ideas and proposals of Innovation Teams and foundational work to demonstrate MDT combinations in practice
Doctrine of Risk
Establish a Doctrine of Risk to improve shared understanding of stakeholder needs and expectations.
Extrapolation Framework
Develop a framework for Extrapolation to support methods by which narrow use cases can be used in broader use cases.
Innovation Teams
Establish forums for sharing information and developing shared strategies for advancement of an integrated drug development and clinical trial process.
Cultivate an Ecosystem
Cultivate a drug development ecosystem that supports drug development sciences and recognizes the public health benefits of medication access.

The true potential of MDTs will only be realized when multiple MDTs are fully integrated, in combination, as a complete toolkit of approaches and methods that can be tailored to a medicines development program to optimize the trial process. And those combinations of MDTs can only be conceptualized, tested, and advanced once the individual MDTs gain some level of acceptance. The strategy, once optimized, will lay out a vision for how individual MDTs can advance from concept, to narrow acceptance, to broad acceptance, and how combinations of MDTs can progress through that same iteration.

Strategic Initiatives

Absent a concerted effort and strategy, the iterative expansion of MDT acceptance is likely to occur organically over the course of many years, perhaps decades. The core of this Initiative is to speed that process and achieve more rapid and clear integration of MDTs and the stakeholders in the ecosystem. The Strategic Initiatives of the Steering Group are key to expediting this acceptance process.

Strategic Initiatives will build on the environment created through four key strategies (detailed below). Leveraging the output of those strategies, the Strategic Initiatives will "put those pieces together" to create real working examples and case studies of how implementation will advance integration. The current environment provides a prime example of how a Strategic Initiative could advance integration. The development of therapeutics and vaccines for COVID-19 is demonstrating the ways in which MDTs—such as RWE, Bayesian statistics, and innovative trial designs—can be leveraged to significantly reduce the time and cost of medicines development and advance public health. A Strategic Initiative to leverage those successes and apply them to expanded areas, such as antimicrobials development programs, is a significant opportunity to normalize and integrate the use of those MDTs.

Strategies

As noted, the success of the various Strategic Initiatives will be positioned and enhanced through four key strategies.

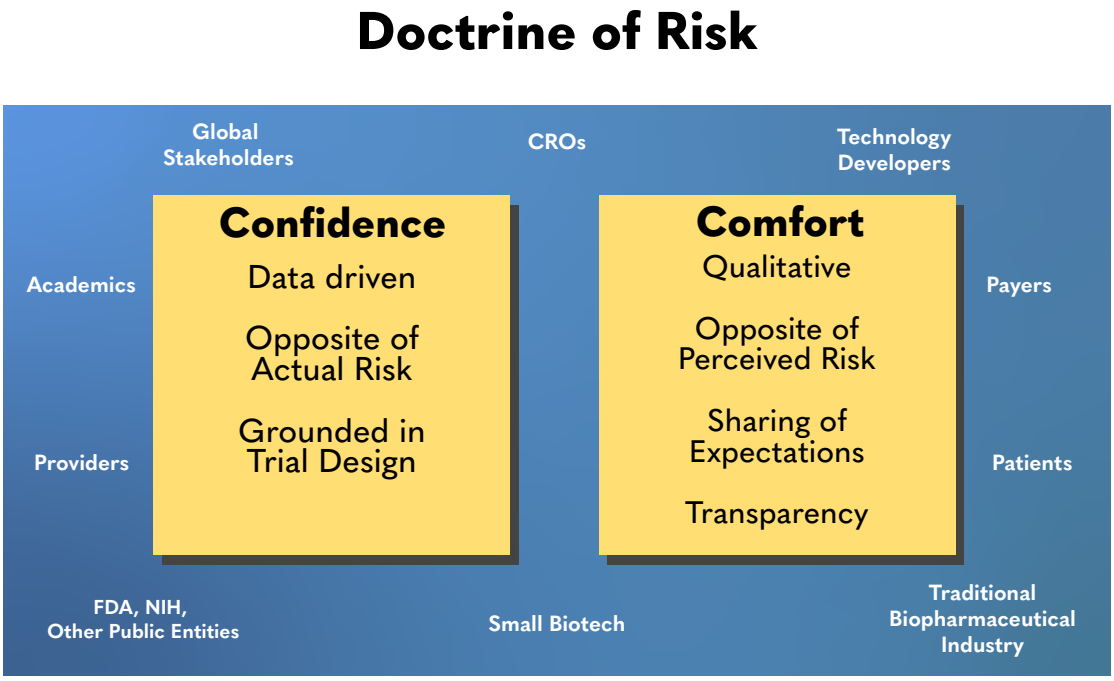
Strategy 1: Establish a Doctrine of Risk to Improve Shared Understanding of Stakeholder Needs and Expectations

The key to efficiently expanding the use and acceptance of MDTs and combinations of MDTs is building **confidence** and **comfort** among all stakeholders, including regulators, pharmaceutical industry, patients, providers, payers, and more. Once confidence and comfort among stakeholders are achieved, they do not remain stagnant; they continue to grow stronger and larger, which is a prerequisite to achieving the end goal of widespread multi-MDT use.

Confidence is a highly quantitative characterization and, in many ways, can be thought of as the opposite of **actual risk**. Confidence is derived from the clinical trial process and evaluation of sound, reliable data. The development of COVID-19 treatment and preventive measures has provided a crystalline example of the relationship between confidence and actual risk, and how these can vary by stakeholder type.

Comfort is a highly qualitative characterization and, in many ways, can be thought of as the opposite of perceived risk. Comfort goes beyond the existence of reliable data demonstrating that a particular use of an MDT works and requires development of an understanding as to why and how that MDT works. Comfort is often grounded in a degree of transparency and is essential to overcoming external factors that have the potential to cast doubt on the reliability of a particular MDT use.

Stakeholder needs and expectations to achieve confidence and comfort will vary by stakeholder groups. A **Doctrine of Risk** that documents those collective needs and expectations will provide critical transparency, which in turn enables the development of strategic initiatives and medicines development practices. This provides stakeholders with confidence and comfort in a fully integrated medicines development ecosystem that utilizes the full array of MDTs.



Strategy 2: Develop a Framework For Extrapolation to Support Methods by Which Narrow Use Cases Can be Applied in Broader Use Cases

Today, most MDTs are used sparingly and in narrow circumstances, such as rare diseases or life-threatening diseases—in oncology, for example. The current experience with developing COVID-19 vaccines and therapeutics has further highlighted this situation as the risks and costs of the disease have driven increased willingness to accept RWE and leverage seamless and adaptive trial principles. Too often, however, successful applications of MDTs are limited by the narrow, rare, or high-risk circumstances in which they were applied.

If true integration of MDTs is to be achieved, stakeholders need to find a systematized way of understanding why MDTs have been successful in those narrow circumstances and how those successes can be extrapolated to broader applications, such as cardiovascular, infectious, and autoimmune diseases. A commonly accepted framework to support that expansion will speed and support the integration of MDTs. The framework will provide a method for assessing both the "seed" (i.e., characteristics of the disease) and the "soil" (i.e., patient characteristics) in successful applications of MDTs and identifying opportunities to select and apply those MDTs in similar "seed" and "soil" with broader application. One way this concept could be reduced to practice is with a systematic, per development program approach to identification of a suite of MDTs that addresses/assesses both "seed and soil" for a given disease category, and then repeats for other disease categories. COVID-related experiences, and prospects to expand COVID-related successes to other critical product categories, will serve as a key opportunity to develop and test such a framework.

"Finding a space to comfortably engage in collaborative public-private partnerships is going to be critically important in speeding up industry's delivery of therapies to patients through improvements in industry productivity and performance, which as we know is under stress."

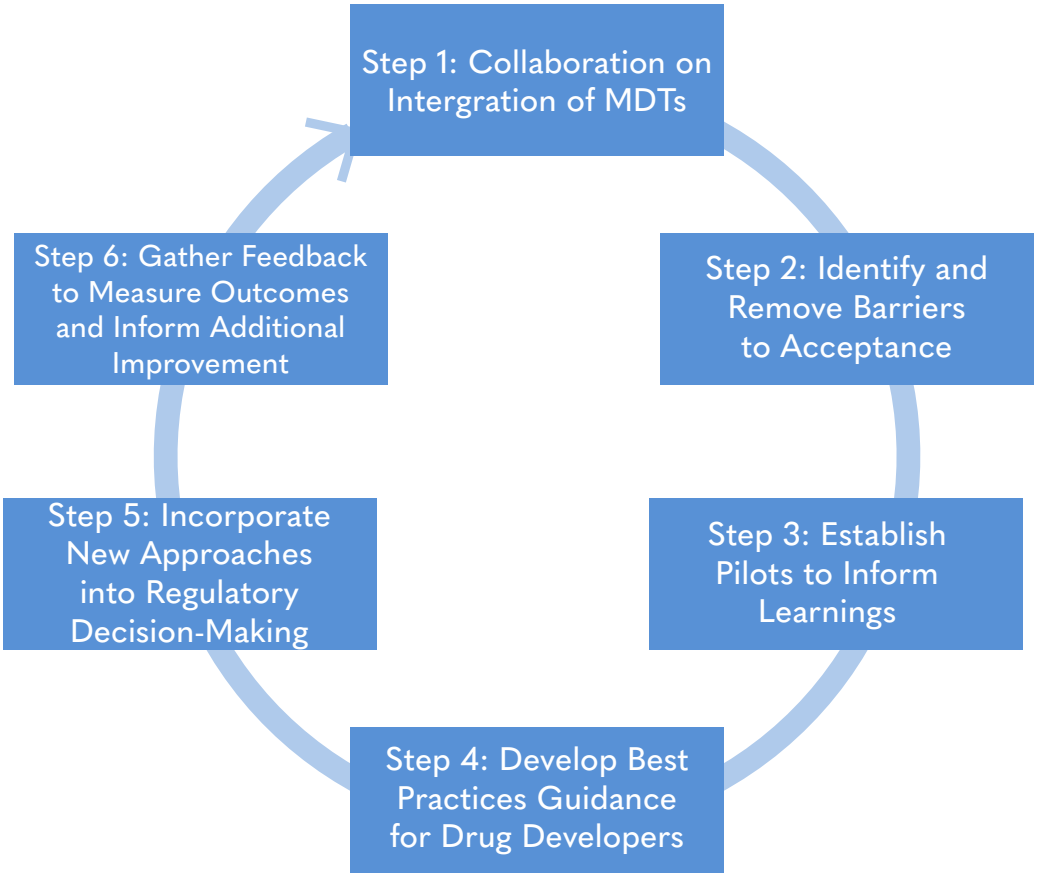
—George Vradenburg, UsAgainstAlzheimer's

Strategy 3: Establish Forums for Sharing Information and Developing Shared Strategies for Advancement of an Integrated Medicines Development and Clinical Trial Process

The long-term goal of the Initiative and this strategy is to create a robust approach that includes a transparent process to collect comprehensive, detailed needs and expectations from all stakeholders up front, routine interim opportunities to gather stakeholder feedback as the process progresses, and the ability to transparently shift direction in a data-driven manner as interim feedback is collected—all with the goal of more rapidly and efficiently delivering medicines that are more valuable to more stakeholders.

A key aspect of creating confidence and comfort among stakeholders is identifying why such lack of confidence and comfort exists in the first place. Limited-duration Integrated Innovation Teams (LIITs), grounded in bringing diverse stakeholders together, will be established to develop and test creative new MDT applications and combinations. Specific to this initiative, there currently (as of December 2020) exist two LIITs: one devoted to RWE and another to Biostatistics. Both LIITs are composed of experts in the fields of RWE and Bayesian statistics, as well as members of the pharmaceutical industry and other key opinion leaders In addition to exploring how to gain confidence and comfort among stakeholders, specifically regulators, both LIITs are also devoted to (i) identifying ways to improve the medicines development ecosystem by expanding and improving upon work already being done in RWE and Bayesian statistics; and (ii) determining how things can be done differently and identifying opportunities to do so. Broadly speaking, the continual process that the LIITs are currently launching is captured in the figure to the right. The LIITs are meant to be highly collaborative, and as members of the LIITs bring to the table their expertise,

curiosity, and willingness to be innovative, the LIITs will eventually be able to develop breakthrough guidance and best practices to reduce barriers to more broadly integrated use of MDTs for the benefit of the entire medicines development ecosystem.



A diversity of stakeholder engagement, perspective, and commitment is critical to the success of the LIITs (and that of the initiative generally). The LIITs are innovation- and creativity-focused forums, and their success in identifying new ways to apply MDTs and gain MDT acceptance is highly dependent on the inclusion of the right stakeholders at the right time. To date, the LIITs have drawn heavily from the biopharmaceutical industry, but their membership has also included academics as well as former and current regulators. Expanded regulator engagement is critical to the success of the LIITs. The LIITs provide a unique forum to engage in open, collaborative discussion of stakeholder interests and concerns and to build a collective understanding of MDTs and their public health value. This collaboration and understanding can foster and expand a culture of shared commitment to developing and delivering safe, effective treatments that meet patient needs. This culture is similar to the ethos within FDA's Oncology Center of Excellence, which prioritizes a shared commitment to development of therapeutics.

[7] FDA's Oncology Center of Excellence: https://www.fda.gov/about-fda/fda-organization/oncology-center-excellence

Strategy 4: Cultivate a Medicines Development Ecosystem that Supports Medicines Development Sciences and Recognizes the Public Health Benefits of Access to Timely, Safe, and Effective Treatments

The table in Attachment A outlines a general strategy for expanded stakeholder engagement at all three levels of the Initiative: Steering Group, LIITs, and general stakeholder community.
Integration will only be achieved within an ecosystem that is receptive to inn
ovation and recognizes the public health benefits of continued access to medicines across all disease states. A deliberate strategy to communicate the imperative public health needs of continued innovation in medicines development and enhanced efficiency in that process is needed to cultivate such an ecosystem. This strategy will focus on broad public communications and awareness, targeted engagement with each stakeholder group in the ecosystem, and specific emphasis on cultivating a more robust academic medicines development community.

To be clear, the academic community is an essential component of a robust medicines development ecosystem. The independence, credibility, and support of the well trained and actively engaged academic community will enable more rapid integration of MDTs, including through input to and participation in the activities outlined in this strategy. A clear, systemic career pathway for academics to learn about the medicines development process, to understand MDTs and their uses, and to study how to enhance the efficiency and effectiveness of medicines development will support more rapid integration. Academic Centers of Excellence in Medicines Development will foster greater innovation and acceptance of MDTs; their research will enhance and drive confidence and comfort among all stakeholders; and a broader base of academic scientists dedicated to medicines development will open a pipeline of talent and expertise that regulators, the biopharmaceutical industry, and health care providers can lean on.

Attachment A

Stakeholder Strategy

Stakeholder integration is a key component of the overall integration objective and distinguishes this Initiative from other ongoing efforts. The chart below provides an overarching framework for a stakeholder integration strategy. Stakeholder groups currently engaged in some compacity are noted in green. Near-term (next 6 months) areas of focused expansion are noted in yellow. Longer-term areas of focused expansion are noted in orange.

The near-term focus (yellow) centers primarily on those stakeholder groups that represent potential barriers to integration, as previously documented, given the importance of engaging those groups early and collaboratively to create an open and constructive dialogue. Those stakeholder groups of immediate focus are regulators, patients, payers, and CROs.

	Stakeholder Integration	LIIT Integration	Steering Group Integration
Traditional Biopharmaceutical Industry	Current/Immediate	Current/Immediate	Current/Immediate
Small Biotech	Near-Term	Longer-Term	Longer-Term
FDA, NIH, and other public stakeholders	Near-Term	Current/Immediate	Current/Immediate
Legislative Policymakers	Near-Term		
Patient Advocates	Current/Immediate	Near-Term	Current/Immediate
Consumers	Longer-Term	Longer-Term	
Providers	Longer-Term	Longer-Term	Longer-Term
Payers	Near-Term	Near-Term	Near-Term
Academics	Near-Term	Current/Immediate	Current/Immediate
Technology Developers	Current/Immediate	Near-Term	Near-Term
Innovative CROs	Near-Term	Near-Term	Longer-Term
Global Representatives	Current/Immediate	Current/Immediate	Current/Immediate
Other Consortia	Near-Term	Near-Term	Current/Immediate
Regulatory Lawyers	Longer-Term		
Other Thought Leaders			

Immediate = 1 month // Near-Term = 1-3 months // Longer-Term = 3-15 months