



gettingstarted

The Medical Research and Development Primer

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DESPITE 21ST CENTURY medical and technological advances, from the decoding of the human genome to stem cell science, from health information technology to targeted cancer therapies, many patients continue to receive the same treatment options offered decades ago. For those who are not so lucky, no options exist at all or available options are highly inadequate.

What's behind the slow momentum in medical progress?

There are many factors, including the complexities of human biology, the serendipitous nature of research, and the structural obstacles that have risen from the ways in which the biomedical research enterprise has grown and evolved over the past 50 years.

But with growing demand for better preventive, diagnostic, and therapeutic options, and broad recognition of the need for a more effective and efficient medical research and development (R&D) system, we are beginning to see transformations in the way we conduct biomedical research. To accelerate this

transformation, the Milken Institute's Center for Strategic Philanthropy (CSP) asserts that we should be more intentional and strategic about how we engage and involve all stakeholders—especially those outside the traditional research establishment.

Medical philanthropy, in particular, has proven to play an outsized role in catalyzing and jump-starting innovation. By investing wisely in improved processes and collaborative research, donors can make relatively high-risk investments that could significantly advance a potential product, move a field of research forward, and increase the likelihood that other parties will also invest.

As part of our effort to realize medical philanthropy's true potential, CSP has created tools and resources to help donors navigate the complex R&D paradigm. We developed the *Getting Started: Medical Research and Development Primer* to provide philanthropists and philanthropic organizations with an outline of the process needed to translate scientific

discoveries into accessible medical solutions. Establishing a clear understanding of the major components of the R&D cycle is a key step in building a high-impact medical philanthropy portfolio. This primer is meant to serve as a companion to our *Giving Smarter: Building a High Impact Medical Philanthropy Portfolio* publication, which focuses on helping donors decide the types of organizations to fund.

At the CSP, we continue to witness the brightest ideas surface when disciplines intersect. CSP's medical philanthropy program, in partnership with our sister center, *FasterCures*, allows us to bring together nontraditional allies who share the goal of bringing medical solutions to patients. It is our goal to facilitate information-sharing across all sectors—from investors to innovators, from researchers to regulators, and from academics to advocates. ***No one can do this alone.*** Expediting cures requires us all to collaborate and pass the baton of innovation seamlessly from one stage of research to the next until it improves patient outcomes and quality of life.

Discovery Research

What is discovery research?

Discovery research, often referred to as “basic research,” is hypothesis-driven and hypothesis-generating research focused on expanding the knowledge base about a disease, without necessarily having knowledge of its potential application to practical problems.

Why is discovery research important?

In many diseases, even the most basic biological questions remain unanswered. Investment in discovery supports efforts to uncover fundamental new knowledge that can then be translated into diagnostic, preventive, and therapeutic benefit for patients, or lead to new concepts in applied medicine.

What are the challenges facing scientists who conduct discovery research?

Academic scientists who conduct most discovery research are under immense pressure to develop studies that can be published—often the measure for career advancement or job security. Yet, discovery is the most uncertain stage in the R&D process. At the onset of a study, it is unclear how long it will take to get results or what the potential impact may be. As funders become more focused on demonstrating tangible results from their grants, discovery researchers may face an increasing pinch in their quests to secure the resources they need.

WHAT ARE THE OPPORTUNITIES FOR PHILANTHROPISTS?

By focusing on academic centers and nonprofit institutions that have the right policies in place to facilitate translation of discovery research into real benefit for patients, philanthropists can maximize the impact of their discovery dollars. For donors without the technical knowledge, human resources, and financial capital to assess recipients on an individual basis, giving through nonprofit medical research foundations provides an opportunity to leverage an already established approach to ensure that funding is allocated well.

Who conducts discovery research?

Discovery research traditionally has been conducted largely by academic research centers, government institutes, and some stand-alone nonprofit research institutions.

Who pays for discovery research?

In the United States, the National Institutes of Health (NIH) and the National Science Foundation fund most discovery efforts in the biological and biomedical sciences, although some support also comes from private philanthropy and industry. Some private philanthropy dollars are channeled through nonprofit medical research foundations (MRFs), intermediary organizations that typically focus on a specific disease area and distribute funds based on expert-informed understanding of that disease’s scientific landscape.

Translational Research

What is translational research? Bench to bedside and back.

To improve human health, scientific discoveries must be translated into practical applications. One of the goals of translational research is to focus on the transition from discovery science to clinical application in a more rigorous and systematic way. In simple terms, translational research involves the process of applying discoveries generated during research in the laboratory, and in animal studies, to the development of trials and studies in humans. However, the process can go the other way. Clinical observations also can inform or drive discovery research, and translational research provides a stepping stone from clinical knowledge back to the laboratory. This iterative process is often called “bench to bedside and back.”

Why is translational research important?

Translational research bridges the gap between promising discoveries in the laboratory and their testing in the clinic. As a scientific discovery moves through the development process, the cost of further advancement increases exponentially. The steps in translational research are designed to ensure that the discoveries that advance into human trials have the highest possible chance of success in terms of both safety and efficacy. Weeding out failures earlier in the process can significantly decrease the overall cost of developing new products.

Data gathered during the translational research stages are essential for getting regulatory approval to market products. In the United States, these data form the basis of an Investigational New Drug (IND) Application submitted to the U.S. Food and Drug Administration (FDA), which is required before a product can enter human trials.

EXAMPLES

- 1 Applying knowledge about the actions of certain molecules in the nervous system to test theories of disease pathways in animal models of a given disease.**
- 2 Testing the prevalence in large populations of a newly discovered biomarker of a rare genetic disease as a preliminary step toward developing a diagnostic test.**
- 3 Observing that certain people have an adverse reaction to a vaccine and working backward to find out what about their disease history or genetic makeup could explain their reaction, with the goal of developing a different vaccine for that subpopulation.**

What are the challenges facing scientists who conduct translational research?

Translational activities may seem to be a natural transition in the medical research process, but that is not always the case. Part of the problem is that translational research frequently requires multidisciplinary and interdisciplinary expertise, while research training and career tracks tend to be compartmentalized. Basic scientists are not generally trained to think of the clinical applications of their work and clinicians are often not taught to formulate research studies based on their clinical observations. Although collaboration between basic and clinical scientists frequently happens, our growing knowledge base and complicated research agenda require a more concerted effort to make a seamless transition between bench and bedside, through translational research.

Conservatism in investments made by government and industry has led to an ever-widening gap—known colloquially as the “Valley of Death”—in funding and support for the kind of research that moves basic discoveries down the path toward products. In addition to the funding gap, academic scientists frequently lack access to the technical infrastructure and specialized expertise—in areas such as regulatory, intellectual property, and privacy issues—that is required to support translational research. Further, the incentive structure for academic scientists tends to reward grant success, publication of novel research results, and patent approval over efforts to move those discoveries toward practical application.

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Who conducts translational research?

A variety of players from both the for-profit and nonprofit sectors conduct translational research. On the industry side, translational research may be conducted in-house at pharmaceutical and biotechnology companies or outsourced to contract research organizations (CROs). On the nonprofit side, specialized translational research institutes created as stand-alone entities or housed within academic institutions often are key centers of translational research activity. Some translational research also is conducted in academic centers and research institutes.

Who pays for translational research?

Funding for translational research traditionally has been a relatively small portion of government spending on medical R&D. Meanwhile, the pharmaceutical industry has been risk-averse, shying away from investing in translational research. Industry-driven translational research activities often have been driven by small biotechnology and pharmaceutical companies, typically supported by investments from venture capital firms.

However, rising attention to the need for more emphasis on converting basic scientific knowledge into potential products led to the creation by NIH in 2011 of a new specialized funding program for translational research, the National Center for the Advancement of Translational Sciences (NCATS). Furthermore, pharmaceutical companies facing patent expirations and a lack of potential products to replace them appear to be showing renewed interest in investing earlier in the development process than they have in the past.

KEY FACTS

- 1 In drug development, the full spectrum of translational research takes three to six years on average.
- 2 Out of every 5,000-10,000 compounds that start off in the drug discovery process, only 250 advance to preclinical testing, and only five advance to clinical development.
- 3 The average cost of all R&D prior to clinical development including basic and translational research is over 700 million dollars.

The need for greater funding of translational research increasingly drives the strategies of MRFs and other nonprofit funders. These include product development partnerships (PDPs), nonprofit organizations that work with partners from the public and private sectors to shepherd products, typically for global health diseases, along the spectrum from discovery research through post-marketing studies. MRFs and PDPs, funded at least in part through private philanthropy, play a significant role in filling the gap between NIH's discovery focused research grants and industry's preferred investment in less risky later-stage development activities. Examples of PDPs are the Cystic Fibrosis Foundation, which yielded the breakthrough drug, Kalydeco, and the Leukemia & Lymphoma Society Therapy Acceleration Program, among others.

WHAT ARE THE OPPORTUNITIES FOR PHILANTHROPISTS?

Giving through nonprofit organizations such as Medical Research Foundations (MRFs) and Product Development Partnerships (PDPs) that support translational research allows individual philanthropists to:

- 1 Leverage the expertise of leading scientific experts within a specific disease or funding area.**
- 2 Advance potential new tools to the point where industry may be willing to take up their development.**
- 3 Fund translational research institutes that focus their expertise on the processes required for translating discoveries into medical solutions, working across diseases.**

In addition to funding product-focused R&D, philanthropists also can have an impact on translational research by supporting efforts to improve the tools and resources available to researchers. This work is done in a variety of institutions and settings, though rarely comprehensively, so each potential recipient should be evaluated individually. Investments could include efforts to:

- 1 Develop better animal models to predict the behavior of compounds in humans.**
- 2 Identify biomarkers to help make testing products more effective and efficient.**
- 3 Create interoperable research databases, comprehensive biobanks, information technology platforms, and data standards and protocols.**

Philanthropists also may want to consider investments in training and career development opportunities to attract and empower new scientists to conduct translational research.

Clinical Research

What is clinical research?

In the context of medical R&D, clinical research is **research in human subjects** aiming toward approved products for use in patients. Pre-registration clinical research for drugs and vaccines is broken into three key phases:

- 1 **Phase I** examines the safety of the product in a very small group of healthy volunteers (20-80 people).
- 2 **Phase II** assesses the efficacy and correct dosing in a larger group of patients (100-300 people).
- 3 **Phase III** tests the product in a much larger, more diverse population to determine broader efficacy, develop usage guidelines, and compare with existing products for the same indication (1,000-3,000 people).

Why is clinical research important?

Clinical trials determine whether a particular product is as effective in people as it is in the laboratory or in animal models, which often fail to adequately mimic human responses. Further, clinical trials provide information on potential adverse reactions or side effects that need to be weighed against the potential benefits.

What are the challenges facing scientists who conduct clinical research?

Clinical research relies on the willingness of both healthy individuals and patients to voluntarily allow scientists access to their bodies, health data, and biological specimens such as blood and tissues. Recruiting a sufficiently diverse set of participants for a given trial can be time-consuming and expensive, as many potential participants are either unaware of the need for volunteers. Likewise, clinical research requires the involvement of diverse and highly skilled physician investigators, and there is a growing recognition that the current workforce is insufficient to meet the development needs of a growing pipeline of products.

Recruiting a sufficiently diverse set of participants for a given trial can be time consuming and expensive.

Additionally, there is no standardized, broadly implemented information technology system to support efficient data collection and analysis in clinical research. Finally, clinical research is the most expensive stage in the R&D process, requiring significant financial resources to conduct.

Who conducts clinical research?

Clinical research is conducted in a wide variety of settings where investigators have access to a patient population, human biological specimens, or clinical data. These include academic health centers, private research institutes, government laboratories, public and private hospitals, practice- or insurance-based researchers and networks, public health departments, and community health centers. On the industry side, some small-scale trials may be carried out directly by the sponsoring company, while most later-stage, large-scale trials are outsourced to CROs. CROs handle all administrative aspects of the trial, including recruiting and training researchers, providing supplies, coordinating study administration and data collection, monitoring adherence to trial protocols, and ensuring the resulting data are clean.

Who pays for clinical research?

Although the probability of success, even if incremental, is greatly increased by the time a potential product reaches the clinical stages of development, the costs of conducting human trials is exponentially higher than discovery and translational research. Government funders do place some emphasis on clinical research; however, this funding is small relative to the need, and support for discovery remains their top priority.

The pharmaceutical and biotechnology industries invest the lion's share of their resources—more than \$50 billion annually—in clinical testing. However, the uncertainty inherent in the process, coupled with rising development costs, has

KEY FACTS

- 1 **Clinical development of a single product, including Phases I through III, takes six to seven years on average.**
- 2 **Only one out of every five compounds that enter clinical trials will be approved for use in patients.**
- 3 **It now takes an average of \$2.6 billion and 15 years to develop and win approval for a new drug, compared to \$1 billion at the turn of the 21st century.**

led many companies and investors to be interested primarily in investing in compounds only after they have an established “proof of concept,” which usually comes in late Phase I or even early Phase II clinical studies. Often, this leads industry to invest primarily in developing so-called “me too” products that offer incremental improvements over existing options.

For diseases where there is not sufficient market opportunity, either because the disease is relatively rare or because the affected population lacks the resources to pay for care, researchers may face additional challenges in raising funds to support clinical development. Although the NIH invests a significant share of its clinical research funding in rare diseases, these resources are insufficient to cover the high costs of seeing a product through the development process. For global infectious diseases of poverty, like malaria and tuberculosis, nonprofit PDPs, like the Global Alliance for Tuberculosis Drug Development and the International Partnership for Microbicides, frequently seek to use philanthropic resources to fill the void.

WHAT ARE THE OPPORTUNITIES FOR PHILANTHROPISTS?

As discussed, although the pharmaceutical industry invests heavily in clinical research, these funds are not always distributed according to the level of patient need. Many diseases lack sufficient market share to incentivize investment by companies that ultimately are responsible for their bottom line. Philanthropic investment in clinical development of new drugs and vaccines for rare and neglected diseases can help to advance life-saving products through the pipeline and create incentives for investment where they otherwise may not exist.

For many global health diseases, Product Development Partnerships (PDP) rely on philanthropic and other funding to support products through the phases of clinical development. Nonprofits and philanthropic funding play a smaller role in funding clinical development outside of global health; however, some Medical Research Foundation (MRF), particularly those with substantial R&D budgets, do provide some support for clinical research activities. Nonprofit groups, supported by philanthropy, also contribute to clinical research by supporting the process.

Such investments include:

- 1 Registries and databases to help connect patients and researchers**
- 2 Improvements in clinical trials infrastructure, technology, and standards to ensure that the data collected through trials is comparable and high-quality**
- 3 Training and career development programs to help build a cadre of capable scientists to conduct clinical trials**

Regulatory Application & Approval

What happens when all of the research is finished?

Once a candidate product has passed through all of the stages of clinical research, the sponsor prepares a package of required data and submits it to the appropriate regulatory agency. In the United States, this package of data, submitted to the FDA, is called a New Drug Application (NDA). Similar packages are required by the European Medicines Agency (EMA) in Europe, the Pharmaceutical and Medical Devices Agency (PMDA) in Japan, and other national regulatory authorities. These agencies review data on safety and efficacy to determine whether the candidate should be approved for use in patients.

In the case of products for use in developing countries, sponsors typically submit a data package to the World Health Organization (WHO) for inclusion on WHO's list of prequalified medicines, which serves as the basis for procurement decisions made by many international organizations and developing country governments.

What kind of follow-up occurs after a product is approved?

As products are made available to an ever-growing population of consumers, sponsors are required to continue to monitor safety issues and report the results to regulatory authorities. In some cases, sponsors also may be required or may choose to conduct formal Phase IV trials to evaluate long-term safety, assess the use of products in certain population groups (e.g., children), or determine optimal conditions for use. Safety issues discovered through Phase IV trials may result in a decision to revoke regulatory approval.

KEY FACTS

- 1 It typically takes between six months and two years for a new drug application to go through FDA's approval process.
- 2 The WHO prequalification process takes between three months and two years.

Nonprofit Actors & Their Roles in the R&D Process

Research and Academic Institutions

Academic institutions are involved throughout the medical R&D process. Academic research laboratories, housed in universities and independent research institutes around the world, typically have focused much of their efforts on discovery research, often funded by the NIH. In addition to increasing general understanding of disease, these institutions contribute to the creation of tools and resources to support R&D efforts.

Programs like the NIH's Clinical and Translational Science Awards are designed to increase the capacity of academic institutions to conduct applied medical research aimed at developing products. Targeted funding from government and philanthropic sources is supporting small amounts of translational research in academic research laboratories. Meanwhile, academic medical centers, which have access to large cohorts of patients, samples, and data, tend to focus their research efforts on clinical development of new products, conducting trials sponsored by industry and government.

Medical Research Foundations

MRFs are nonprofit organizations that fund medical research in a specific disease or set of diseases. Some MRFs focus exclusively on R&D, while others engage in a broader set of activities that may include patient services, advocacy, and family/caregiver outreach, among others. Within their research programs, effective MRFs typically engage a set of external

scientific experts to provide advice on the development of research strategies and the selection of grantees. Often, these strategies focus on gaps not typically funded by government or industry, including translational and early clinical research.

These groups can serve as a reliable source of funds for novel, high-risk research that might not be able to compete successfully for public funds. MRFs also may invest in development of tools and resources, including patient registries and training programs to encourage young scientists, among others.

Product Development Partnerships

PDPs, nonprofit organizations that work with partners from the public and private sectors to shepherd products through the development process, are major drivers of medical R&D in global health. PDPs typically draw their funding from government and philanthropic sources and partner with academic institutions, government agencies, and industry to conduct their activities. Many do not have any physical research facilities, relying instead on their partners to conduct R&D activities.

These groups operate more like pharmaceutical companies than do most MRFs, managing the development strategy and process for a portfolio of candidates ranging from translation through clinical research stages. Given the resource constraints found in most countries where the diseases they target are located, PDPs also frequently invest in research infrastructure and other tools to support their efforts.

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