

Patient Engagement in Pharmaceutical Research and Development

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ABSTRACT

There has been a significant change in how trial sponsors engage with patients, shifting from the traditional approach of maintaining distance from patients and treating them as passive subjects in clinical trials to one of recognizing them as active partners across the drug research and development continuum. In advancing this shift, patients and their advocates are taking active roles in discovery and pre-clinical research, in the design and execution of clinical trials, and in leading post-market evaluation activities. Patient groups are increasingly developing and strategically deploying assets to ensure the perspectives of their constituents are included in clinical research, leading to the development of treatments that meet the needs of patients while decreasing risk and accelerating the therapy development process. As this form of patient engagement becomes more common, evidence of its success and positive impact on all stakeholders is mounting.

Keywords: Patient, Clinical trials, Traditional approach, Research and development

KEY POINTS

1. Patients and the groups representing them have valuable insights and assets that can be strategically deployed to de-risk and accelerate pharmaceutical research and development.
2. The value of patient engagement in pharmaceutical research and development can be ascertained through an economic model based on expected net present value (ENPV), which is based on improved patient experience and elimination of protocol amendments in clinical trials.

INTRODUCTION

There has been a significant change in how trial sponsors engage with patients, shifting from the traditional approach of maintaining distance from patients and treating them as passive subjects in clinical trials to one of recognizing them as active partners across the drug research and development continuum [1]. As patient organizations, industry leaders, and regulatory officials work to achieve patient centricity and develop mechanisms for ensuring the patient voice is incorporated into all aspects of therapy development, evidence of the positive impact of patient engagement is mounting [2].

This paper presents the background and historical context for this evolution and evaluates the opportunities for all stakeholders, especially therapy developers, to leverage a

variety of novel approaches to patient engagement for future success.

THE ADVENT OF MODERN PATIENT ADVOCACY ORGANIZATIONS: HISTORY AND CONTEXT

Patient groups, also referred to as patient advocacy organizations, disease advocacy groups, or voluntary health agencies, have been a significant part of the disease and medical research landscape for decades. Some of the earliest and most recognized models include the American Lung Association (founded in 1903) [3], the American Cancer Society (founded in 1913) [4] and the American Heart Association (founded in 1924) [5]. Through these and other national non-profit organizations, patient advocates have pursued missions of research, education, advocacy and support. Primary areas of programmatic focus for these early groups included raising philanthropic dollars to fund basic and translational research, public-facing disease awareness and education, policy advocacy and direct patient support.

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The patient advocacy landscape began to shift significantly in the 1970s and 1980s. The Juvenile Diabetes Research Foundation was formed in 1970 [6] and the AIDS Coalition to Unleash Power (ACT UP) was established in 1987, with the patient community coming together to demand a more urgent government and industry response to the AIDS crisis [7].

In the 1990s, breast cancer advocates followed the example set by the AIDS community when the Komen for the Cure organization (founded in 1982) launched their Race for the Cure program in 1991 [8] in an effort to collectivize and harness the energy of a growing patient and caregiver community. The National Breast Cancer Coalition (NBCC), founded in 1991 [9], launched a campaign to bring the patient directly into the design and leadership of research programs, resulting in the creation of the Department of Defense (DoD) Breast Cancer Research Program [10].

The NBCC also pioneered the concept of engaging patient advocates directly in research programs, developing a scientific and advocacy boot camp for patients called Project LEAD [9]. This program has produced a cadre of skilled breast cancer research advocates to serve on the National Institutes of Health study sections, DoD and Patient-centered Outcome Research Institute (PCORI) [11] leadership and grant review committees and as active partners in industry sponsored drug research and development [12]. This model has been adopted by multiple patient organizations [13,14]. As a result of the continued efforts of cancer patient advocacy organizations, the Congressionally Directed Medical Research Program (CDMRP) at the DoD has expanded to cover research for multiple types of cancer, while mandating the involvement of patient advocates on grant review panels [15].

At the same time that there was an increased emphasis on policy advocacy to drive priorities of government research programs, the patient advocacy community began to develop its own capacity to identify and help fund promising research. The 1990s saw the formation of an array of patient-focused non-profit organizations that raised philanthropic dollars to fund research and research advocacy programs specifically designed to accelerate discovery and therapy development [16], including the Prostate Cancer Foundation [17] and the Michael J Fox Foundation for Parkinson's Research [18]. These organizations saw a need and opportunity to exert influence over the research enterprise in their respective disease areas, establishing scientific and medical advisory boards and bringing research and clinical expertise in-house by hiring experts to join their increasingly professionalized staffs [19]. These trends set the stage for the dramatic shift that was to come.

PATIENT ENGAGEMENT TODAY

Many of today's patient advocacy organizations have developed sophisticated models and programs to ensure

active patient engagement across the continuum of research and therapy development [20]. Having shed the early 20th century mind-set of patients as passive beneficiaries of the research and development ecosystems, these organizations are focused on proactive and engaged efforts to participate in and drive the process of ensuring better outcomes for their constituents. The array of sophisticated, innovative initiatives undertaken by many groups today includes launching patient registries and conducting natural history studies; funding translational and early-phase clinical research programs; designing trials; developing novel trial infrastructure; leveraging venture philanthropy to drive therapy development; and conducting policy advocacy aimed at the evolving regulatory environment [21,22].

One important way in which patient organizations can contribute to drug development is by helping to fill basic research knowledge gaps about the natural course of disease progression through the conduct of natural history studies [23]. This is especially critical in areas of rare and less common diseases. Patient groups like Parent Project Muscular Dystrophy (PPMD) [24], the Cystic Fibrosis Foundation [25], Friedrich's Ataxia Research Alliance [26], and the Platelet Disorder Support Association [27] are just a few of the pioneers in establishing sophisticated patient registries [28] (some with US Food and Drug Association [FDA] funding support) [29] that can be mined for natural history studies to establish an evidence base against which drugs can be developed.

While many patient organizations have traditionally used philanthropic support to fund basic research, these groups are increasingly directing their funding toward more translational and clinically-based research designed to prime the pump for therapy development, better identify patients who can benefit from specific therapies, and accelerate bringing new products to patients. Using targeted research grants, patient groups have funded clinical consortium efforts to develop better models and conduct early-phase clinical trials. These programs are designed to help close the gap between basic science and successful therapy development, assisting in 'de-risking' the work of industry [30]. For example, the Multiple Myeloma Research Foundation has established a Translational Research Network [31] aimed at establishing pre-clinical models and evaluating new drug targets.

Patient groups are moving quickly to leverage their expertise and knowledge about what their constituencies most want and need from new therapies by working with trial sponsors to select novel endpoints for trials, evolve clinical trial inclusion/exclusion criteria and develop validated outcomes measurement tools. Groups that have been active in these efforts include PPMD [32], with its pioneering efforts to define patient preferences and move away from the traditional 6-minute walk test outcome measure; the LUNgevity Foundation, with its Project Transform [33];

and Friends of Cancer Research, which worked with the American Society for Clinical Oncology to issue recommendations for broadening eligibility criteria for clinical trials in cancer [34].

These activities have evolved with patient organizations launching sophisticated clinical trials of their own, engaging multiple industry and academic partners in a robust clinical development network to accelerate therapy development. These trials have served as opportunities to address serious shortcomings in the expense and delay associated with traditional clinical development paradigms and has helped to popularize novel trial designs such as basket trials, umbrella trials, and master protocols. Examples of this work include the Pancreatic Cancer Action Network's Precision Promise initiative [35], the Leukemia and Lymphoma Society's Beat ALM project [36] and the National Biomarker Development Alliance's GBM AGILE [37]. FDA leadership has publicly embraced this evolution [38].

Increasingly, patient groups have also looked to more direct engagement in drug development, leveraging a venture philanthropy model of investing directly into partnerships with industry that, if successful, could not only bring new products to patients but also yield a return on investment for the non-profit to help further advance its mission. Pioneers in this arena include the Cystic Fibrosis Foundation [39], the Juvenile Diabetes Research Foundation [40] and the Leukemia and Lymphoma Society [41].

Finally, recent years have seen a dramatic increase in the amount and type of public policy efforts undertaken by patient organizations, with specific focus on advancing patient engagement within the regulatory arena through direct engagement with the FDA, as well as through legislative initiatives to support opportunities for enhanced patient participation in drug development. These efforts were on display throughout the process of the reauthorization of the Prescription Drug User Fee Act (PDUFA) and the enactment of the 21st Century Cures legislation.

THE DRUG DEVELOPMENT ENTERPRISE RESPONDS: INDUSTRY AND REGULATORS

The medical products development field (drugs, biologics, devices) has traditionally approached patients as subjects, with drug developers and regulators generally reliant on the input of scientific and clinical experts (referred to as Key Opinion Leaders (KOLs)) as an appropriate proxy for identifying what patients need and want [42]. In this traditional model, companies generally approached patient engagement as a commercial enterprise [43], with emphasis on accruing for late-stage trials (medical affairs), designing marketing activities (patient education), and providing testimonials to assist with regulatory reviews and reimbursement (policy advocacy).

Patient organizations, reflecting the desires of their patient constituencies to be viewed as 'KOLs in their own right' and frustrated by the slow pace of drug development and the desire to see clinical trials and regulatory reviews that more accurately reflect the needs and desires of patients, began to advocate for transformative changes in the process of therapy development with a specific focus on changing the regulatory dynamic.

Industry, eager to respond to this trend and find ways to more systematically bring the views of their patient communities to regulators for inclusion in product reviews, began to implement shifts in corporate culture and make significant structural changes to their traditional models of patient engagement. Decisions by Sanofi and Pfizer to hire senior level patient officers [44,45] and by companies like Celgene to develop on-going cooperative programs with patient organizations (Patients' Partners Program) [46] provide high profile examples of companies elevating patient engagement into the ranks of corporate leadership. Smaller biotech companies also experimented with developing patient partners and best practice activities to bring patient perspectives further upstream into their discovery and clinical development programs. In 2016, BIO (the trade organization representing biotech companies) published a report to assist its members and other stakeholders in developing these types of activities [42]. Research and development of medical products is undergoing a transformation to enhance patient involvement across the enterprise [47].

Recognizing the importance of enhancing and institutionalizing these activities, all stakeholders see on-going opportunity to leverage the process for reauthorizing the PDUFA. With the negotiations and commitment letters issued for PDUFA V and VI [48] and with the passage of the landmark 21st Century Cures Act, additional progress in completing the shift toward enhanced patient engagement throughout the entire drug development continuum was made. The FDA recently launched its Patient Focused Drug Development (PFDD) initiative, convening 24 public meetings organized by disease state from which a series of Voice of the Patient (VoP) reports were generated [49]. The FDA is encouraging patient organizations to host externally-led PFDD meetings [50], as the FDA turns its attention to issuing a series of guidance documents for stakeholders about incorporating the patient voice directly into product reviews [51].

OPPORTUNITIES: MAKING THE CASE FOR PATIENT ENGAGEMENT

There is emerging consensus among patient advocates, industry leaders, and regulatory officials that patient engagement early and often throughout the therapy development continuum can provide significant value to all stakeholders [52]. Specifically, the collective acceptance of the PFDD initiative is based on the view that strategic

incorporation of patient perspectives (especially what they most want and need from therapy for their specific conditions) can inform clinical development strategies, improve the quality and efficiency of clinical trials and lead to more effective and meaningful therapies [53,54].

In 2014, the Clinical Trials Transformation Initiative (CTTI), a multi-stakeholder, public-private partnership between Duke University and the FDA, launched a project that recognized the significant opportunity to improve the clinical trials enterprise and enhance participation by patient groups in the work of trial sponsors. The project sought to identify barriers to meaningful engagement of patients in the development of therapeutic products, while identifying and developing consensus for best practices around the various important roles patients can play in improving the entire

enterprise, from study endpoint selection that reflects outcomes of importance to patients, to recruitment and retention in clinical trials and post-marketing safety evaluation.

CTTI developed a set of recommendations [55] and tools appropriate for a regulatory environment that provide clarity around how, when, and by whom patients or patient groups should be engaged during the therapy development process, and which patients or patient groups should be engaged. The recommendations introduced practical guidance to partnership optimization for sponsors, investigators, and patient groups and were endorsed by Dr. Janet Woodcock, Director of the FDA Center for Drug Evaluation and Research, as a positive step in advancing the field of patient-focused drug development (Table 1).

Table 1. Recommendations on best practices for effective patient group engagement [55].

Recommendation	Details and actions
<i>For all stakeholders</i>	
Engage the “patient voice” by establishing partnerships from the beginning of the research and development program to improve trial design and execution	• Include the perspective of patients (i.e., the “patient voice”) in the early stages of disease targeting. • Sponsors benefit by a clearer, more focused understanding of unmet need, therapeutic burden, opportunities for expanding indications, and better targets. • Patients benefit by less burdensome study protocols and more meaningful and relevant endpoints, increasing the likelihood they will participate in the trials or potentially help to develop a meaningful treatment for their disease.
From the start, clearly define the expectations, roles, and responsibilities of all partners, including the resources being committed, data being shared, and objectives of the program	• It is important to clearly delineate the roles of partnership and clarify the goals and objectives of the collaboration. • Expectations about the role of PG consultation and input should be clarified at the start of the collaboration. • PG input may be taken into account when determining the objectives of a clinical program or development of a protocol, research sponsors must balance that input with scientific understanding as well as business and regulatory needs.
Build the trust required for successful partnerships by being transparent and trustworthy, following through on commitments, and honoring confidentiality	• All stakeholders should be open, transparent and honor commitments to the development program. • Confidentiality Agreements (CAs) and Non-Disclosure Agreements (NDAs) allow sharing of sensitive information with PGs. • Expectations about the role of PG consultation and input should be clarified at the start of the collaboration.
Involve the expertise of multiple partners for a broader perspective to mitigate risk and enrich pipeline development	• PGs should be involved with multiple research sponsors to increase the pipeline of therapies in development. • Sponsors should engage with more than one PG in a particular disease area to ensure that a representative patient perspective is reflected in the input obtained.

Manage real or perceived conflicts of interest by establishing policies that require full disclosure, transparency, and accountability	- There are no FDA laws, regulations, or guidelines explicitly prohibiting early engagement with PGs. - It is important to clarify which kinds of interactions with PGs are permissible and which ones might violate FDA regulations or fraud, abuse and other regulations. - The bottom line is that research sponsors can engage with PGs in planning and conducting clinical trials. - Each type of PG engagement will have its own contractual rules and parameters to mitigate risk.
For research sponsors (academic and industry)	
Integrate into your ongoing research and portfolio planning an assessment of PG expertise, assets, and value to your program	- The primary drivers for PG engagement are achievement of project milestones, corporate culture, and therapeutic area/vertical business unit interaction. - Research sponsors need to develop and execute a comprehensive roadmap for substantive PG engagement. - Research sponsors should consider identifying a single point of contact from the company or institution that has a sufficiently broad view of the internal dynamics of the organization.
Match PG expertise and assets to the specific needs and phases of your R&D programs	- Research sponsors should recognize differences in the skills, experience, and capabilities of PGs. - Currently there are no industry-wide tools used to select a PG. - It is imperative to assess PG expertise, interests, organizational capacity, and relationships.
Ensure that PGs are essential partners throughout the R&D process and not token voices	- Research sponsors should recognize that the most successful partnerships with PGs are those in which both entities are full partners at the outset, working toward the same goals from different perspectives. - The patients' voice as communicated by PGs is key to understanding the day-to-day effects of the condition and the acceptable benefit-risk trade-off of treatment.
For consistency, establish guiding principles and clear lines of communication to facilitate a fit-for-purpose process for collaborating with PGs	- Sponsors should establish and document best practices for engaging with PGs, including how to approach them, the legal requirements for working with them, and a template for master services agreements. - Elements of the work practice may include a database of previous collaborations, required documents, and clear lines of communication.
Measure the impact of PG engagement	- Though no standard metrics exist for PG engagement across industry, it is recommended that research sponsors establish expectations up front on how to measure the effectiveness of the partnership. - A regular assessment of satisfaction related to objectives, expectations and success of strategies is recommended.
Establish ongoing relationships with PGs and communicate openly with them on a regular basis	- Study teams should communicate with them regularly throughout in the development program. - It is also important to maintain regular communication with PGs even when there is no study news.
For patient groups	
Proactively identify, engage and bring the patients' voice to stakeholders relevant to your R&D interests	- Recognize that there are limits to what any one PG can accomplish alone. - To be successful in partnerships, you must build and sustain that trust to maintain your credibility among the constituents who rely on your group for dependable information.

Promote your value as an essential partner by maximizing and articulating your expertise and assets	- PGs should know what they can offer research sponsors and have information and/or data that clearly articulate their value proposition. - Through active, continuous engagement in the development program, PGs can demonstrate a unique value to their academic and industry partners.
Deliver your expertise and assets to sponsors throughout the entire R&D process	- PGs should express the patient perspective as early as possible and throughout the development process—during basic and translational research, preclinical and clinical trial planning and implementation, the regulatory process, and the post-market period. - The degree to which the PG can provide grants to selected academic investigators and participate in a variety of forms of funding with industry partners and even well-vetted venture philanthropy partners will help position the PG as a key player in the field.
Select sponsors who have a product or program with significant promise for your constituents and who are committed to engaging in a meaningful way	- PGs should ensure that they have a “finger on the pulse” of the preclinical landscape in order to maximize opportunities and ensure that they are viewed as valuable partners for sponsors. - The PG should consider establishing a scientific review process in order to have an independent ability to evaluate the science being presented.
Manage real or perceived conflicts of interest by establishing policies that require full disclosure, transparency and accountability	- PGs should create written policies to clarify their position on accepting funds from industry sponsors, purchasing company stock and other activities that might be perceived as generating a conflict. - To manage internal and external conflicts of interest (COI) effectively, PGs should fully disclose relationships with industry sponsors. - To help PGs navigate the complex web of decisions and opportunities, it is recommended that they prospectively develop a “Guiding Principles” document.

CA: Confidentiality Agreement; COI: Conflict of Interest; FDA: Food and Drug Administration; NDA: Non-Disclosure Agreement; PG: Patient Group; R&D: Research and Development

Implementing a sustainable and effective approach to patient engagement and engaging patients early and often in the research and development process are both critical to delivering on the promise of less costly, more efficient and effective therapy development to more rapidly deliver better treatment options to patients [56]. As companies continue to implement these strategies, there are several areas of focus that can assist in maximizing the success of these efforts.

Most importantly, effective patient engagement requires the full commitment of everyone in an organization—from corporate leaders to researchers and developers to those involved in commercial and marketing efforts. Corporate senior leaders are increasingly embracing patient engagement as the way of the future [57].

It is vital for those within a corporate structure to engage effectively with patient organizations and individual patients; there needs to be a focus on evolving corporate culture to enable this engagement. Training should be undertaken to ensure that all within the company understand the purpose and importance of engaging with patient organizations and individual patients. Additionally, traditional legal, contracting and communication functions should be evaluated to ensure that they are designed to allow

for appropriate and effective interaction with non-profit entities and individual patients.

It may be necessary to evolve corporate structures to allow for seamless integration of patient engagement across internal divisions and teams, shifting from patient interactions with only commercial and marketing teams to integration in research and development, clinical operations, and clinical innovations. It may make sense to leverage the expertise of patient alliance staff by more directly linking them to clinical development activities. It is likely that current siloed functions may need to be expanded and connected to allow for maximum success.

Finally, it should be recognized that implementing strategic patient engagement within a company (across its portfolio and pipeline) will take time and requires a long-term commitment, with the appropriate investment of resources (human capital as well as financial).

ASSESSING THE FINANCIAL VALUE OF PATIENT ENGAGEMENT

Patient advocates and regulators are convinced of the value of patient engagement efforts. Many in industry accept the assumption that incorporating appropriate patient

engagement strategies will be worth the investment; however, some seek tangible data to support this hypothesis. To provide this evidence, efforts to define and quantify the return on investment have been documented in the second phase of CTTI's patient group engagement project.

In 2016, CTTI presented a conceptual model to estimate the financial value of patient engagement based on expected net present value (ENPV), which integrates the key business drivers of cost, time, revenue, and risk into a summary metric for project strategy and portfolio decisions (**Figure 1A**) [2,58]. This helped the team outline what it would take to show the impact of a decrease-to-launch time and the total cost of the clinical trial enterprise as a framework for valuing patient engagement, as it has been difficult to make the fiscal value proposition. As a case example, CTTI assessed the impact of patient engagement on ENPV for a typical oncology development program entering phase 2 or phase 3. CTTI established that for a pre-phase 2 project, the

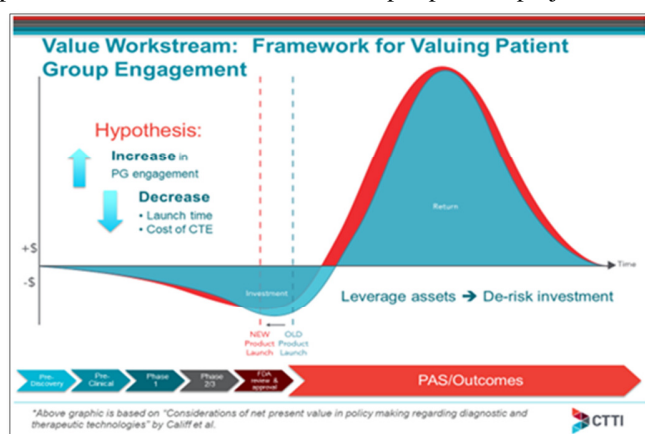


Figure 1A. Framework for valuing patient group engagement [58].

CONCLUSION

Patients and their advocates are taking more active roles in discovery and pre-clinical research, in the design and execution of clinical trials and in leading post-market evaluation activities. Patient groups are increasingly developing and strategically deploying assets to ensure the perspectives of their constituents are included in clinical research, leading to more rapid development of treatments that meet the needs of patients while decreasing risk and accelerating the therapy development process. Critical assessment of corporate culture and restructuring may be necessary to effectively engage patients early and often in the research and development continuum, as well as development of a structure to assess return on investment through emerging economic models.

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Selig: Nothing to report.

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cumulative impact of a patient engagement activity that avoids one protocol amendment and improves enrolment, adherence, and retention is an increase in net present value (NPV) of \$62MM (\$65MM for pre-phase 3) and an increase in ENPV of \$35MM (\$75MM for pre-phase 3). Compared with an investment of \$100,000 in patient engagement, the NPV and ENPV increases can exceed the investment by 500-fold. This ENPV increase is the equivalent of accelerating a pre-phase 2 product launch by 26 years (16 years for pre-phase 3). The work determined that risk-adjusted financial models can assess the impact of patient engagement by using a combination of empirical data and subjective parameter estimates, which correlate patient engagement activities with the potential to avoid protocol amendments and/or improve enrollment, adherence, and retention (**Figure 1B**) [2]. The third phase of CTTI's work is focused on developing tools to help sponsors identify high-value patient engagement activities for investment.

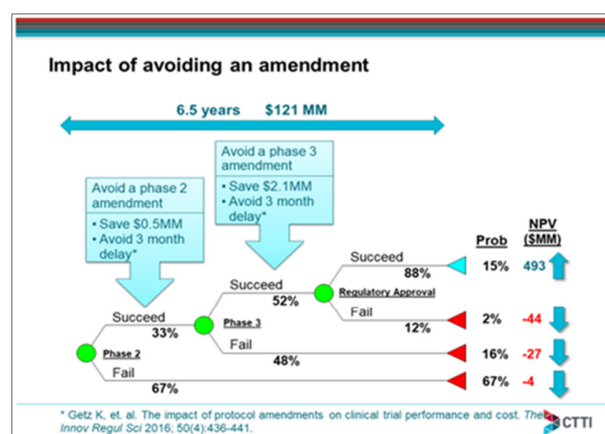


Figure 1B. Impact of avoiding a protocol amendment [2].

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