Framework for Aligning Research Sponsors and Patient Groups on Methods for Engagement

Eisenstein EL[1], Getz KA[2], Harker M[1], Hesterlee S[3], Patrick-Lake B[4], Levitan B[5]
[1]Duke Clinical Research Institute, Durham, NC, USA, [2]Tufts University, Boston, MA, USA, [3]Myotonic Dystrophy Foundation, San Francisco, CA, [4]Duke University, Durham NC, USA, [5]Janssen Research & Development, LLC, Titusville, NJ, USA

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Introduction

- Policymakers are implementing initiatives to promote direct patient involvement across all medical product (drug and device) development phases [1].
- However, there is little guidance as to which patient group engagement methods are most or least effective in given scenarios and lead to greater or lesser value for patients, sponsors, and society in the context of medical product development.
- In prior work, the Clinical Trials Transformation Initiative's (CTTI's) Patient Groups and Clinical Trials (PGCT) Project Team identified a set of 31 patient group engagement methods [2].
- Working in conjunction with the Drug Information Association, this team surveyed patient groups, academia, and industry perceptions regarding patient group engagement [3].
- The study found that between-group differences in perceived benefit hampered the pursuit of patient group-industry partnerships and reduced their likelihood of success.

Objectives

(1) Develop a method for characterizing the relative value associated with each CTTI engagement method from both the patient group and sponsor perspectives; and
(2) Use this approach to identify patient group engagement methods that may have both high benefit and low investment for patient groups and sponsors, in a rare disease scenario.

Methods

Defining Patient Group Engagement Methods

- We created value-based definitions for each of the 31 patient group engagement methods previously identified by CTTI's) Patient Groups and Clinical Trials (PGCT) Project Team [2].
- We associated each method with one or more of five drug development phases: prediscovery, preclinical, trial phases 1–3, FDA review, and postapproval (Table 1).

Benefit–Investment Framework Development and Demonstration

- Patient groups and industry sponsors may have different perceptions regarding patient group engagement value drivers. To industry sponsors, value is generally related to five key value drivers: revenue, cost, time, risk, and intangibles.
- To summarize these relationships, we developed a framework consisting of the investment required to implement a specific engagement method and the expected benefit that might accrue from investing in that method.
- We divided each dimension into two components (high and low investment, high and modest benefit) resulting in four benefit–investment categories for each stakeholder: (1) high benefit–low investment, (2) modest benefit–low investment, (3) high benefit–high investment, and (4) modest benefit–high investment.
- We then demonstrated the use of our the CTTI-PGE framework by assigning the 31 engagement methods to one of the four benefit–investment categories using our working group's understanding of how each engagement method may likely influence the five value drivers in a typical medical product development scenario. Assignments were made from both the patient group and industry sponsor perspectives using the most likely scenario for each method.
- We defined low investment as <$100,000 and high investment as ≥$100,000. We subjectively weighted all possible benefits that may be derived from an engagement method based on our assessment of how patient groups and sponsors would perceive benefits; other users of the framework will apply their own criteria for benefits.

Results

- The greatest potential use of the 31 patient group engagement methods occurred during trial phases 1–3. However, there were significant opportunities for engagement before clinical trials began—during prediscovery and preclinical—as well as after FDA approval.
- Engagement methods were initiated (first used) in every drug development phase, but while methods could be initiated during prediscovery and preclinical, most were initiated only in phases 1–3.
- Table 2 describes how the 31 patient group engagement methods impact upon value drivers for both stakeholder groups in a typical medical product development scenario.
- Overall, we believe patient groups and industry sponsors would agree on 21 (68%) of the benefit–investment category assignments. Those were the 10 methods with high benefit–low investment, 9 methods with modest benefit–low investment, and 2 methods with high benefit–high investment (Table 2). No engagement methods were agreed on as modest benefit–high investment from both patient group and industry perspectives.
- The group of high benefit–low investment engagement methods could serve as a starting point for partnerships between patient groups and sponsors because they have the best benefit-to-investment ratio for both partners.

Discussion

- For patient groups and industry sponsors who are beginning to collaborate on treatments, our results provide examples of where to invest attention and resources toward meaningful engagement.
- The 10 engagement methods rated as high benefit–low investment in our example form the basis for a patient group engagement starter toolkit in conjunction with the organizational assets inventory.

Limitations

- Our study is limited by our subjective input and assessment from a small group of professionals engaged in the promotion of patient engagement in clinical research. We did not conduct formal surveys for the benefit–investment assessment in a rare disease, and we used a simple system that considered only the most common outcomes for each engagement method.
- Other stakeholders might select different boundaries for high versus low investment and high versus modest benefit depending on their position within the therapeutic space and the capital situation of their organization.

Conclusion

- We have introduced a tool for patient groups and sponsors to use in the evaluating the use of patient group engagement methods throughout the medical product development lifecycle, and we have shown how the use of this tool can highlight potentially valuable engagement methods for both patient groups and clinical research sponsors by identifying areas of collaboration.
- Work by other investigators is needed to demonstrate how the use of this tool can lead to value creation for both stakeholder groups across multiple therapeutic areas and study contexts.

REFERENCES:
1. Hunter NL, O'Callaghan KM, Califf RM. Engaging Patients Across the Spectrum of Medical Product Development: View From the US Food and Drug Administration. JAMA. 2015:1-3. PMID:26584067. doi:10.1001/jama.2015.15818.
2. Clinical Trials Transformation Initiative. CTTI Recommendations: Effective Engagement with Patient Groups Around Clinical Trials. Available at: http://www.ctti-clinicaltrials.org/files/PatientGroups/PGCTrecs.pdf. Accessed May 9, 2016.
3. Smith SK, Selig W, Harker M, Roberts JN, Hesterlee S, Leventhal D, et al. Patient Engagement Practices in Clinical Research among Patient Groups, Industry, and Academia in the United States: A Survey. PLoS One. 2015;10(10):e0140232. PMID:26465328. doi:10.1371/journal.pone.0140232.

Table 1. Patient Group Engagement Methods Across the Medical Product Development Lifecycle

PD=Prediscovery · PC=Preclinical · P1-3=Phase 1,2,3 trials · FDA=FDA Review/Approval · PA=Post Authorization/Market

	Engagement Method	Definition	PD	PC	P1-3	FDA	PA
1.	Input regarding interest of research question to patient community	PG provides feedback based on experience, community surveys, focus groups, or data in its registry on whether or not the planned clinical endpoints are meaningful and practical for its patient population	■				
2.	Providing data on unmet need and therapeutic burden	PG determines to what degree a planned therapeutic might meet the needs of the patient community, by any of a variety of means including surveys, focus groups, natural language processing of online communities, and tapping existing internal knowledge	■	■	■	■	
3.	Fundraising and direct funding for research to identify target molecules	PG contributes funds directly to a sponsor to support early research and development or exploratory activities, with or without a negotiated return on investment. When a return is negotiated, this activity usually falls under the umbrella of venture philanthropy	■	■	■		
4.	Facilitating collaboration with NIH, FDA, Congress, academia and other PGs	PG maintains dialogue between program or review officers and PG stakeholders, provides education and evidence, and engages in advocacy around policy issues	■	■	■		
5.	Funding characterization of the disease and relevant mechanisms of action	PG sponsors research at either academic institutions or sponsor organizations to better identify targets and mechanisms of action and potential therapeutics	■				
6.	Helping define study's eligibility criteria	PG provides feedback based on experience or its registry data to determine if the eligibility criteria contemplated for the study protocol are practical and appropriate for its patient population		■	■		
7.	Providing translational tools (assays, cell and animal models, biosamples, biomarkers, etc.)	PG provides access to or otherwise facilitates (e.g., organization of a consortium) the development and validation of biomarkers	■	■			
8.	Natural history database and patient registry support	PG supports or otherwise facilitates the conduct of natural history studies and/or the aggregation, mapping, and storage of natural history data through a registry or other means	■	■	■	■	■
9.	Input on meaningful clinical endpoints	PG supports or otherwise facilitates (e.g., organization of a consortium) the development and validation of endpoints		■	■		
10.	Conducting or participating in benefit-risk and patient-preference studies	PG facilitates or performs preference studies to support benefit-risk assessment, or provides feedback from surveys, focus groups, or experience on benefit-risk preferences of the patient community			■		
11.	Assistance regarding informed consent form/process	PG provides feedback based on experience, community surveys, or focus groups on the content of the informed consent form			■	■	■
12.	Working with FDA regarding benefit-risk and draft guidance	PG provides data and insights or performs benefit-risk assessment to FDA to inform draft guidance on study design, meaningfulness of selected endpoints, and benefit-risk		■			
13.	Accompanying sponsor to pre-IND FDA meeting to advocate for study	PG attends pre-IND and other FDA meetings with sponsor to provide additional input on issues such as study design, meaningfulness of selected endpoints, and benefit-risk		■			
14.	Fundraising and direct funding for research and trial operations support	PG contributes funds directly to a sponsor to support ongoing research activities, with or without a negotiated return on investment. When a return is negotiated, this activity usually falls under the umbrella of venture philanthropy			■		■
15.	Advise on study recruitment plan	PG provides feedback on recruitment plan based on geographic, demographic, and symptom profile data in its registry or database and/or from experience of the PG with prior trials and site capabilities			■		■
16.	Provide peer advocates during informed consent process	PG staff or volunteer advocate supports trial participants in understanding the informed consent process			■		■
17.	Assistance in selecting and recruiting optimum clinical sites	PG provides data or insights related to patient heat mapping, Centers of Excellence, key opinion leaders, performance that supports patient satisfaction and timely recruitment and that results in patient retention and high-quality data			■		
18.	Clinical infrastructure support	PG creates or supports clinical networks, training programs, equipment purchases, or other types of infrastructure that support clinical trial activities			■		■
19.	Helping educate and motivate patient community and recruit for trials	PG raises awareness and educates patients about clinical trials; PG uses registries or databases to identify patients who meet trial criteria			■		■
20.	Providing patient feedback on participant experience	PG acts as clearinghouse for feedback from participants on sites and study experience to help manage issues proactively and better plan for future studies			■		
21.	Serving on data and safety monitoring boards (DSMBs)	PG staff or volunteer advocate participates on DSMB to provide perspective on benefit-risk			■		■
22.	Input for any trial adaptations or modifications	PG staff or volunteer advocate provides input on protocol and feasibility; may participate in simulation exercise and suggest improvements that eliminate barriers to participation or minimize burden on patients			■		
23.	Accompanying sponsor to milestone meetings; e.g., after phases 2 and 3	PG staff or volunteer advocate accompanies sponsor to milestone meeting to provide feedback on data			■		
24.	Providing public testimony at the FDA Advisory Committee and other FDA hearings	PG staff or volunteer advocate, while acting as an independent agent, provides defensible data on symptom burden, experience with existing treatments, and benefit-risk preferences at FDA hearings				■	
25.	Preparing submission for newborn screening for rare disease when appropriate	When appropriate, PG assists in the submission of newborn screening for a rare disease if it is believed that (1) the treatment being reviewed, if approved, can change the outcome for patients diagnosed early with the disease; (2) sufficient understanding of the disease's natural history is established, and (3) a newborn screening test for the disease is available and reliable both for affected and unaffected infants				■	■
26.	Serving on postmarket surveillance initiatives	PG participates in postmarketing study steering committees or working groups that review safety signals					■
27.	Helping return study results to participants	PG enables, supervises, or otherwise orchestrates the return of study results to participants or works with sponsor to develop a summary in lay language					■
28.	Copresenting results	PG participates with sponsor on the presentation of study results at various venues to support united front and positive view of collaboration outcome					■
29.	Publications and communications regarding results	PG raises awareness of study outcomes with the general public, including the patient community and stock holders/investors via written, electronic, or video media about study outcomes					■
30.	Feedback on how patient community views results	PG provides feedback to sponsor regarding patient community view of study results by any of a variety of means including surveys, focus groups, and tapping existing internal knowledge					■
31.	Working with payers regarding reimbursement	PG provides evidence and advocacy in support for coverage or its expansion					■

Abbreviations: DSMB=data safety and monitoring board; IND=investigational new drug; PG=patient group
Drug development lifecycle legend: PD=prediscovery; PC=preclinical; P1-3=phases 1–3; FDA=FDA approval; PA=postapproval

Table 2. Value Perception Characterization

High benefit-Low investment · Modest benefit-Low investment · High benefit-High investment · Modest benefit-High investment

	Engagement Method	Impact on Value Drivers	Value Perception: Patient Group	Value Perception: Sponsor
1.	Input regarding interest of research question to patient community	Facilitating benefit-risk assessment, focus groups, and survey studies requires small investments for patient groups and industry sponsors while the potential benefits of this information are great. The resulting information may improve study designs, leading to shorter study durations, lower risk, and lower costs.	High benefit–Low investment	High benefit–Low investment
2.	Providing data on unmet need and therapeutic burden	Providing data on a known, unmet need requires a low investment for patient groups with modest potential benefit to sponsors and with a high associated risk investment on their part should they decide to proceed.	Modest benefit–Low investment	Modest benefit–High investment
3.	Fundraising and direct funding for research to identify target molecules	Funding target molecule identification requires a significant investment for patient groups with low probability of success. However, the benefit-to-investment ratio is larger for sponsors due to the minimal investment required on their part even if the likelihood of success is low.	Modest benefit–High investment	High benefit–Low investment
4.	Facilitating collaboration with NIH, FDA, Congress, academia and other PGs	Facilitating government dialogue requires a small investment for patient groups and sponsors. However, there are few benefits from this work as the probability of translating results into product development improvements is low.	Modest benefit–Low investment	Modest benefit–Low investment
5.	Funding characterization of the disease and relevant mechanisms of action	Further characterizing a known disease typically requires a significant investment for patient groups but has only modest incremental information for sponsors. Still, the benefit-to-investment ratio is high for sponsors due to their minimal investment in this work.	Modest benefit–High investment	Modest benefit–Low investment
6.	Helping define study's eligibility criteria	Assisting in the definition of study eligibility criteria requires little investment for patient groups and sponsors but may have great benefit by more precisely defining the study population, providing a potential to improve the study design and reduce study duration, costs, and risks.	High benefit–Low investment	High benefit–Low investment
7.	Providing translational tools (assays, cell and animal models, biosamples, biomarkers, etc.)	Providing translational tools requires a significant investment for patient groups with low probability of benefit for sponsors because such tools likely requires significant development costs before acceptance by regulators.	Modest benefit–High investment	Modest benefit–Low investment
8.	Natural history database and patient registry support	Providing additional natural history and patient registry information requires a significant investment for patient groups but has only modest incremental information of value for sponsors.	Modest benefit–High investment	Modest benefit–Low investment
9.	Input on meaningful clinical endpoints	Providing input on meaningful clinical endpoints requires small investments for patient groups and sponsors while the potential benefits of this information are great if study designs can be improved.	High benefit–Low investment	High benefit–Low investment
10.	Conducting or participating in benefit-risk and patient-preference studies	Conducting patient studies requires a larger investment with the potential for providing valuable information that will impact study designs.	High benefit–High investment	High benefit–High investment
11.	Assistance regarding informed consent form/process	Patient group assistance in developing informed consent forms requires a minimal investment and can have great benefit for sponsors if study enrollment and retention are increased.	High benefit–Low investment	High benefit–Low investment
12.	Working with FDA re benefit-risk and draft guidance	Working with the FDA on a draft guidance may require both significant time and resources for patient groups. Still, the benefits will be high if this information can be used to improve the likelihood of product approval.	High benefit–High investment	High benefit–Low investment
13.	Accompanying sponsor to pre-IND FDA meeting to advocate for study	Attending FDA meetings with sponsors requires a minimal investment for patient groups and sponsors with modest benefit to improve the likelihood of product approval.	Modest benefit–Low investment	Modest benefit–Low investment
14.	Fundraising and direct funding for research, trial operations support	Contributing to trial operation funds typically requires a significant investment for patient groups with low probability of benefit because the likelihood of study success is uncertain.	Modest benefit–High investment	Modest benefit–Low investment
15.	Advise on study recruitment plan	Patient group assistance in developing study recruitment plans requires a minimal investment and can have great benefit for sponsors if enrollment is enhanced and retention is improved.	High benefit–Low investment	High benefit–Low investment
16.	Provide peer advocates during informed consent process	Patient group assistance in obtaining informed consent requires a small investment and can have great benefit for sponsors if more patients are enrolled and retained.	High benefit–Low investment	High benefit–Low investment
17.	Assistance in selecting and recruiting optimum clinical sites	Patient group assistance in site selection and recruitment requires a small investment but can greatly benefit sponsors if these sites are able to rapidly enroll patients leading to reduced study times and lower costs.	High benefit–Low investment	High benefit–Low investment
18.	Clinical infrastructure support (2 groups: patients and researchers)	Patient group provision of clinical infrastructure support is expensive and typically has only modest value to sponsors unless is has an immediate effect on study enrollment and duration.	Modest benefit–High investment	Modest benefit–Low investment
19.	Helping educate and motivate patient community and recruit for trials	Patient group assistance in trial recruitment and promotion requires a modest investment and can provide great value to sponsors if enrollment is increased, study duration is reduced, and fewer costs are incurred.	High benefit–Low investment	High benefit–Low investment
20.	Providing patient feedback on participant experience	Serving as a clearinghouse for patient experience feedback typically requires a small investment for patient groups but only yields modest benefits for sponsors unless this information can be used to change study designs.	Modest benefit–Low investment	Modest benefit–Low investment
21.	Serving on data and safety monitoring boards (DSMBs)	Serving on DSMBs is a small time investment for patient groups but does not have great value for sponsors because the impact on study value drivers is uncertain.	Modest benefit–Low investment	Modest benefit–Low investment
22.	Input for any trial adaptations or modifications	Providing protocol input on a standard trial requires a minimal investment for patient groups; however, the benefits for sponsors may be only modest as the trial is ongoing and most major study design decisions have been made.	Modest benefit–Low investment	Modest benefit–Low investment
23.	Accompanying sponsor to milestone meetings; e.g., after phase 2 and 3	Attending milestone meetings requires a small time commitment for patient groups and creates little value for sponsors as this likely results in no changes to the value drivers.	Modest benefit–Low investment	Modest benefit–Low investment
24.	Providing public testimony at the FDA Advisory Committee and other FDA hearings	Providing testimony at FDA meetings requires a small time commitment for patient groups and creates only modest benefit for sponsors because there is little potential impact on the likelihood of product approval.	Modest benefit–Low investment	Modest benefit–Low investment
25.	Preparing submission for newborn screening (NBS) for rare disease when appropriate	If the criteria for preparing NBS submission (refer to Table 1, item 25) can be met, both the investments required and the potential benefits for future product development are great; however, the magnitude of investments and benefits are highly imprecise.	High benefit–High investment	High benefit–High investment
26.	Serving on postmarket surveillance initiatives	Serving on postmarket surveillance initiatives requires a small investment of time for patient groups and typically creates only modest value for sponsors because the products have already been approved and most development costs have been incurred.	Modest benefit–Low investment	Modest benefit–Low investment
27.	Helping return study results to participants	Helping return study results to patients requires a small investment for patient groups with high potential benefits. But for sponsors, the investment is greater and the benefits are largely intangible.	High benefit–Low investment	Modest benefit–High investment
28.	Copresenting results	Copresenting results requires minimal investment for patient groups and sponsors but creates only modest immediate benefit with little to no impact on value drivers.	Modest benefit–Low investment	Modest benefit–Low investment
29.	Publications and communications regarding results	Publication and communication of results to a larger audience requires a small investment that may create significant value if it leads to increased product sales.	High benefit–Low investment	High benefit–Low investment
30.	Feedback on how patient community views results	Obtaining feedback on how the patient community views study results may require a significant investment for patient groups; however, this information may also have great value for both patient groups and sponsors if it leads to greater understanding.	High benefit–High investment	High benefit–Low investment
31.	Working with payers regarding reimbursement	Providing coverage advocacy with insurers requires a small investment of time for patient groups; however, this information may be beneficial for patient groups and sponsors if coverage is expanded.	High benefit–Low investment	High benefit–Low investment

Abbreviations: DSMB=data safety and monitoring board; IND=investigational new drug; NBS=newborn screening; PG=patient group

DCRI COMMUNICATIONS, MAY 2016