



## Patient Group and Clinical Trials Project

Executive Summary of the PGCT Expert Meeting  
held January 21 – 22, 2015

Fairmont Hotel Washington DC

**CTTI MISSION:** To identify and promote practices that will increase the quality and efficiency of clinical trials

Materials from the Patient Group and Clinical Trials Expert Meeting, including agenda, participant list, and presentations, are available on the Clinical Trials Transformation Initiative website at: <https://ctti-clinicaltrials.org/patient-groups-and-clinical-trials-expert-meeting/>

Publication Date: DRAFT version 0.2

## BACKGROUND AND ISSUES

Over recent years, patient groups (PGs), defined here as patient and disease advocacy organizations, voluntary health agencies, public health organizations, and their affiliated members, have been increasingly recognized as equal partners in the research enterprise, especially in the important field of clinical trials.

The inception of the CTTI Patient Groups and Clinical Trials (PGCT) project was at a January, 2013 meeting of CTTI and PG representatives, who agreed that, while key stakeholders have declared their commitment to create a more effective model for engagement among research sponsors, investigators, and PGs leading to better clinical trials, no evidence-based best practices, or even commonly accepted ones, currently exist for PG involvement at the many phases of the clinical trial continuum.

The CTTI PGCT Expert Meeting was convened on January 21-22, 2015, by the project team [<https://ctti-clinicaltrials.org/our-work/patient-engagement/patients-groups-clinical-trials/>]. Representatives of diverse stakeholders in the clinical trial enterprise (CTE) – PGs, Industry, Academia, Investigators, and Government/Regulators — were invited to the Expert Meeting to provide critical perspectives and ask challenging questions toward overcoming barriers and developing best practices for PG engagement with sponsors of researcher.

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## EXPERT MEETING OBJECTIVES

The objectives of the January 2015 PGCT Expert Meeting and Workshop were the following:

- Define consensus principles for PG engagement that take into consideration the perspectives of Industry, PGs, and Academia, using case studies of successes and barriers
  - Share evidence and key findings from a 3-way stakeholder assessment of PG engagement in the clinical trial process
  - Gain understanding of the FDA Rules of Engagement and various Conflict of Interest (COI) issues
  - Solicit attendee feedback on evidence to inform recommendations that can further enhance the value, to all stakeholders, of mutually beneficial partnerships to engage PGs as fully as possible in the complete spectrum of the CTE
  - Solicit feedback on benchmarking, metrics, and value of patient engagement in clinical trials for research sponsors
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## Review of Evidence – PGCT Literature Review, and Stakeholder Survey and Interviews

In 2014, the PGCT Project conducted a literature review, and commissioned an independent survey and structured interviews of stakeholders, gathering evidence to characterize the current intersections among patient advocates and Industry and Academia. **Wendy K. D. Selig, President and CEO, Melanoma Research Alliance (MRA)** described the key findings to attendees of the PGCT Expert Meeting.

Among the critical takeaways from the literature search was that the trust placed in PGs by patients is second only to that of physicians. The literature search found almost no empirical data to define or optimize key factors for successful PG relationships, and no accepted metrics with which to support the value proposition of such relationships for Industry and Academic sponsors.

The independent survey to gather respondents' best practices and barriers to PG engagement in therapy development and clinical trials was sent to stakeholders identified from meeting rosters and mailing lists of CTTI and the Drug Information Association (DIA). There were 244 respondents: 75 from Academia, 119 from Industry, and 61 from PGS. Of the 119 Industry respondents, only 43 (36%) reported that their organizations were currently working with PGs, and 39 had no plans to engage with PGs in future.

Important findings based on the survey included the following:

- For Industry respondents, the primary drivers for PG engagement are corporate culture and therapeutic area/vertical business unit.
- For Academic respondents, the primary drivers for PG engagement are opportunities to gain funding, either nationally-sponsored or PG funded, and to abide by the funding guidelines stipulating patient advocate participation or engagement in various research processes.
- Industry tends to delay PG engagement until late in the development of therapy: 80% of Industry respondents reported engagement with PGs at Phase III, but only 35% at Phase I, and 15% during discovery and preclinical development.
- From Industry respondents, the barriers to PG engagement cited most often were insufficient tools for identifying and engaging the relevant PGs, uncertainty about how to engage, internal resistance and lack of buy-in, lack of funding, and what the respondents perceived as PGs' lack of sophistication around the CTE.
- From Academic respondents, the barriers to PG engagement cited most often were lack of funding, misaligned objectives/priorities/incentives, and the lack of tools for identifying and engaging with PGs.
- From PG respondents, the barriers to engagement with Industry included unclear processes for engagement; sponsors' lack of understanding of the benefits of partnering with PGs, and lack of transparency or openness.

- There were disparities between the perceptions of PGs and those of Industry and Academic sponsors as to what services PGs bring to clinical trials. PG respondents reported contributing support during Industry interactions with payers, assistance with tissue banking, funding for research, and publicity/dissemination of study results at significantly higher rates than Industry respondents reported taking advantage of these contributions.
- Both Industry and Academic respondents cited their own institutions' bureaucratic internal processes; unwillingness to share information; and lack of understanding of the benefits of PG engagement as having negative impact on engagement.

In follow up to the surveys, a qualitative scientist conducted 32 semi-structured interviews with 10 PG leaders, 12 Industry sponsors, and 10 Academic investigators. In general, interview participants reported best practices and barriers for PG engagement that closely matched those cited in the survey.

From the PGCT literature search, survey, and interviews, CTTI identified barriers that were cited consistently, and taking into account solutions suggested by interview respondents created draft recommendations on best practices for effective engagement with PGs between Industry and Academic sponsors in clinical trials. The draft recommendations were presented to the Expert meeting participants by Wendy Selig on behalf of the project team.

There is evidence that sponsor collaboration with PGs around clinical trials is increasing in frequency, and that many of the barriers are modifiable. There is further work to be done on *defining the metrics and models with which to assess the value and impact*.

## Session I: Background/Landscape

Session I presentations were the FDA's perspective on the roles of PGs in the approval process for new therapies; a review of the progress and key findings to date of the CTTI PGCT Project; and an example of a company's success-based best practices for PG engagement in clinical trial design and in trial operations.

In the opening address of the Expert Meeting, **Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER)**, emphasized that PGs can leverage advocacy to have substantive impact on the development of treatment, no matter what the disease. She urged that PGs be well prepared with detailed knowledge of the science and natural history of the disease, know who and where their patients are, who the scientific and clinical experts are, what is the current state of therapy, and what sponsors are planning research and for what potential new treatments. Because of the high failure rate of new drugs, Dr. Woodcock advised that PGs not advocate for any single therapy, but instead work on improving and accelerating the clinical trial ecosystem overall.

Dr. Woodcock described numerous roles and activities for PGs to consider, for

engagement in the clinical trial enterprise:

- The FDA encourages **PGs to conduct disease registries and natural history studies**, which can significantly inform trial design based on the understanding the variability of symptoms and tests over time. With natural history data, PGs can help to devise the duration of treatment and follow-up necessary in order for the protocol to show treatment effect.
- PGs can **fund basic research** directed at learning the pathogenesis of disease, which is still a complete unknown for many diseases.
- PGs should learn from their constituent patients what the therapeutic gaps are, and then make certain that the clinical research community understands what **symptoms are not controlled and what patient needs are not met** by the existing treatments.
- PGs should mine the scientific literature and clinical trial registries to learn what compounds are in preclinical development, and what compounds are currently in clinic.
- Funding from PGs, at any stage of treatment development, will always be critical, considering that the cost of in vitro and preclinical safety testing alone can surpass \$500K for a small molecule and is usually much higher for biologics or gene therapy.
- If the PG has cultivated a group of interested doctors and other experts, those key opinion leaders (KOLs) can be tapped to help write the protocol and conduct the trial.
- If a patient-reported outcome (PRO) is validated to measure effect or tolerability, PGs should **advocate for its inclusion along with the study endpoints routinely selected and defined by doctors and sponsors in the field**. The FDA has run qualification processes for PROs, and would welcome PGs' sharing qualified PROs and their validation data, allowing them to be used in multiple trials and provide a basis for comparison across treatments.
- PGs have **the ability to help recruit and, through ongoing patient support, to keep patients in the trials**. Assuming they have registry data, PGs understand who and where the eligible patients are for the trial.
- The PGs should work to become known as a **ready source of reliable information** to their constituent patients who are considering a clinical trial.
- PGs could **submit draft guidance**— as Parent Project Muscular Dystrophy (PPMD) has done for muscular dystrophy — as a way to inform the FDA, sponsors and investigators about how patients think trials for their disease should be designed, — what to study and for how long, the range of tolerable risks for a given level of benefit, and what PROs and other endpoints are meaningful.

**William J. Tunno, Director of Global Patient Advocacy & Professional Relations at Boehringer Ingelheim** listed his recommendations for Industry sponsors working to optimize PG engagement, based on long his experiences at

building such relationships. The following key points were echoed by other speakers, and by attendees in the interactive discussions and the breakout sessions:

- Companies need a comprehensive roadmap for substantive PG engagement from early research and development (R&D), through clinical development, manufacturing and packaging, marketing, and managed markets.
- Companies just beginning to engage with patient advocates must understand the disease landscape and understand where patients go for information — is it to academics, peers, other PGs? What other sponsor are engaged in developing treatments in the same disease space?
- The company needs a designated lead for PG engagement to ensure a consistent and comprehensive advocacy approach across all departments.
- Companies must establish goals, frequency of contact with the PG, and metrics of the results. Their legal and regulatory departments must be consulted to ensure compliance with the company's guidelines and procedures.
- Because each PG can do different things in the disease space, bringing them together can unearth common goals and stimulate new ideas. For example, bringing together the different stakeholders working on myelofibrosis (MF) allowed them to settle on common definitions, so that the ways of talking about MF became more consistent. Further, Mr. Tunno's company, with an academic partner and help from PGs, developed a clinical trial education tool that helped an MF trial recruit 32 new sites and 64 new patients in one month.
- When engaging with PGs, the company needs to know each group's priorities and their past and present programs, as well as their strengths, whether in policy, finance, or research. Mr. Tunno stressed the importance of taking care that small groups – which are often the case for rare diseases – not feel pressured to engage in efforts beyond their capacity.
- PGs can serve as a trusted media outlet: when press releases about the disease, trials, and new treatments are issued by PGs and academics, patients and families seek them out and read them.

Following Mr. Tunno's address, Wendy K.D. Selig summarized the findings from the PGCT Project's literature search and from the stakeholder survey and interviews regarding PG engagement in clinical trials (See [Review of Evidence](#), above).

Regarding the difficulty that PGs have engaging multiple companies in a shared advisory capacity, Mr. Tunno responded that when his organization partners with multiple sponsors and PGs in oncology/radiology, his selling point is that if the various companies come together to help the PG, each company will benefit for years to come from the resulting collaborative data.

One attendee mentioned that the European Patient's Academy on Therapeutic

Innovation (EUPATI) is also working on PG engagement. She stressed the importance, particularly given that much of Industry has global outreach, of stakeholders in the US being aware of the work going on elsewhere in the world.

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## Session II: Identifying Partners for Clinical Trials

Session II of the PGCT meeting explored the ways in which Industry and Academic sponsors can identify PGs whose activities and assets make them attractive potential partners; how PGs can demonstrate their attractiveness for collaborative opportunities with sponsors, and how PGs can identify likely Industry and Academic partners.

Discussing how PGs can evaluate their own assets and capacity for partnering with Industry, **Margaret (Meg) Heim, Worldwide Lead of Advocacy for Cardiovascular and Immunoscience, Bristol-Myers Squibb (BMS)**, said that in her organization, collaborations with PGs must be based on common interests such as providing patient education and disease awareness, improving access to treatment, and shaping public policy to increase diagnosis, improve quality, and access to care. BMS policy mandates respect for the advocacy organization's independence, and no return-on-investment (ROI) metric may be done with regard to any potential engagement with PGs.

She listed the following key questions that sponsors must address in order to assess PGs for future collaboration:

- Which PGs working in one of the company's disease areas have objectives aligned with the company's?
- Does the PG look to influence policy, increase patient access to treatment, expand reimbursement, influence health technology assessment (HTA), empower individual patients?
- At what point does the company want to collaborate with PGs – in clinical trials development, disease education, policy?

Ms. Heim echoed earlier speakers' contention that PGs have a potential role in all stages of the clinical trial cycle. Typically, companies talk to PGs hoping to understand what it feels like to be a patient with the disease. Ms. Heim reminded the attendees that in any therapeutic area, many of the top basic scientists and KOLs are working in Industry to develop these drugs; this is their life's work, and they want to partner for the long run with PGs who can help them bring the right treatments to patients.

Ms. Heim urged PGs to collaborate with other advocacy groups in the same disease space so that their collective strengths can increase their chances for successfully attracting Industry, Government, and Academic partners.

She noted that Industry looks closely at any and all public information about potential advocacy partners. PGs were advised to consider carefully how their websites reflect their mission, goals, and focus, because how the PGs are

perceived is through their websites, publicly identifiable data, and publications. To illustrate her point, Ms. Heim shared findings of three consultants' assessments of advocacy organizations, commissioned by BMS: From an independent analysis of the web sites and other publicly available information of 12 different PGs and physician associations involved in cardiovascular disease, the company learned that research funding, access to care, and education for patients and healthcare providers (HCPs) were the high priorities of these third party groups. In a second assessment, to understand the global rheumatoid arthritis (RA) patient community, the company learned which PGs working on RA have strong ties with the medical/professional associations, which have direct engagement with government agencies and payers, and which PGs were engaged in regional coalitions to capitalize on shared resources.

Ms. Heim emphasized that regardless of annual budget, a small PG can have a large impact based on their strengths and a focused message. A PG may grow its reputation by finding its niche in a neglected area, such as patient and caregiver support.

Ms Heim noted that even a small PG may have tremendous leverage based on their advocate KOLs. The committed thought leaders who volunteer for a PG may have access to a strong network of collaborative research. In an analysis for her company of the publication history of KOLs in peer-reviewed journals and presentations at US, Japan, and EU conferences and congresses; it was clear that the KOLs in the US have international reach by virtue of being highly integrated in global RA research.

**G. Sitta Sittampalam, PhD, (National Center for Advancing Translational Sciences [NCATS], National Institutes of Health [NIH]** spoke about The Learning Collaboratory (TLC), a partnership of the University of Kansas (KU), the Leukemia & Lymphoma Society (LLS), and NCATS with the goal of identifying new drug therapies for patients with rare blood cancers.

To illustrate the translational capabilities of such a partnership, Dr. Sittapalam described an initiative to repurpose an agent used for 25 years in treating patients with RA. Through a collaboration by the National Heart, Lung, and Blood Institute (NHLBI) and NCATS, the drug auranofin was found to selectively kill chronic lymphocytic leukemia (CLL) cells. Auranofin had long been FDA-approved for RA; thus, the necessary safety and preclinical data were already available. FDA clearance was obtained for a trial of auranofin in patients with refractory CLL. The TLC engaged a clinical research organization (CRO) and was able to progress from the drug screening to administration to CLL patients in only 11 months.

Although its development for CLL ceased when it became clear that more active compounds were available for CLL, auranofin also proved to have activity against mantle cell lymphoma (MCL), and TLC will partner with a qualified CRO to manage the MCL proof-of-concept (POC) trial from site selection through the end of study and final reporting. Dr. Sittampalam explained that while the CRO may provide regulatory advice, one of the full TLC partners (KU) will serve as IND holder.



Dr. Sittampalam noted that the different strengths that each partner brings to a collaboration such as TLC are critical to the partnership's success: the Government partner's skill in product development-focused translational research, the PG's large and sophisticated advocacy program, each partner's network of KOLs, industrial scale screening and discovery platforms, and vast experience with pharma and public-private partnerships.

**Jun Xu, MD, (The Therapy Acceleration Program™ [TAP], Leukemia & Lymphoma Society)** described the Blood Cancer Research Partnership (BCRP), part of LLS's Therapy Acceleration Program (TAP) to achieve novel therapies faster. TAP has four focus areas: (1) a biotechnology accelerator co-funded by TAP with small biotech firms to help get discoveries to POC trials; (2) an Academic concierge program, fully funded by TAP; (3) special initiatives; and (4) clinical trials programs, including the BCRP. Dr. Xu noted that this year, as an institution, LLS has passed the \$1 billion budget mark for funding research, while TAP has invested \$80 million in research funding, with \$100 million committed.

The BCRP was designed to address two problems around involving patients with cancer in clinical trials: 80% of patients with cancer are treated in their communities, many unable to travel to tertiary centers where trials are concentrated; and trial enrollment presents a huge bottleneck, with estimates that only 5% of patients with hematologic cancers participate in clinical trials.

The two partners in BCRP are LLS and the Dana Farber Cancer Institute (DFCI). The goal of BCRP is that patients with leukemia, lymphoma, and myeloma should be able to enroll in innovative trials near where they live. All of the sites are community-based, she noted, but each has the infrastructure – biostatistical and data management capabilities and dedicated staff — to conduct clinical trials with rigor.

In BCRP trials, the LLS provides infrastructure — for example a program manager dedicated to BCRP, plus some support for data management, site monitors, and biostatisticians. The LLS does not directly fund the clinical trials that are approved by BCRP; instead, trial funding is from various sites, with some from Industry partners and some funded as investigator initiated trials.

Per the partnership agreement, she said, both LLS and BCRP can propose trials for consideration, and trials are chosen by committee. In reviewing and selecting clinical trials, the LLS and DFCI must agree that the trials are innovative and well-designed, and that the BCRP sites are capable of running them successfully.

**Ronald J. Bartek (Friedreich's Ataxia Research Alliance [FARA])** related a case study illustrating the dramatic impact that PGs can have in bringing new therapy to patients, regarding the CEO of a small biotech who approached him a few years earlier with promising compounds for Friedreich's ataxia, a disease with no current treatment options. Since their initial meeting, FARA has played multiple critical roles:

- FARA's chief scientific officer had developed the best assay to test

compounds for effect on mitochondrial function, and so was able to identify the biotech's most active and most potent candidate molecules, which he recommended for further investigation.

- To fund development of the compound, FARA helped the biotech/sponsor secure \$4.5 million from a FARA research grant, direct investment by FARA, and a grant from the Muscular Dystrophy Association.
- FARA identified a NIH mechanism that awarded the biotech/sponsor more than \$2 million worth of preclinical work to select the candidate molecule and allow it to move to clinical trials.
- Accompanying the sponsor to their pre-IND meeting, FARA's explanation to the FDA of the patient burden in Friedreich's ataxia, and the acceptable risk to have *any* treatment, proved to be essential.
- The company sought the input of FARA's KOLs and leadership, and consulted FARA's natural history database, in designing the Phase I and II protocols.
- The company was able to recruit and enroll patients from FARA's patient registry.
- For the pivotal trial of the compound, the required 60 patients were enrolled at three of FARA'S 12 partner sites, in only 2 hours and 43 minutes.
- FARA will go with the sponsor to the FDA, to support their application for an NDA.
- FARA has already helped the company secure fast track status for accelerated FDA review.

**Joel Beetsch, PhD, Vice President of Patient Advocacy, Celgene,** acknowledged that a few years earlier, an evaluation showed that his organization was engaging with PGs only at Phase 3, and specifically for trial recruitment. Celgene has since developed collaborations with PGs that span the life of a drug development program, such as the following:

- Celgene partners with LLS, both in the TAP and in Quest for Cures, a series of LLS Request for Proposals (RFPs) to support early basic and preclinical research for potential treatment of hematological cancers. Quest for Cures exemplifies one way in which a PG with significant resources and scientific expertise can help a company engage with the larger disease community.
- Celgene is partnering with the International Multiple Myeloma (IMMF)'s Black Swan Research Initiative™ (BSRI™) to investigate Celgene products in combinations with other companies' drugs, in order to push the disease down as far as possible, maybe even to achieve cure.
- Celgene developed the marketed product Istadax® (romidepsin), for T-cell lymphomas in a private-public relationship with the National Cancer Institute for the Institute's help with scientific and clinical development.
- Celgene works closely with PGs to develop and validate PROs that match QoL indices, so that approved labeling makes clear what it really means to

patients to get a particular product that, for example, reduces the number of transfusions required or reduces spleen size.

- With the Chordoma Foundation, Celgene was able to engage the FDA in discussions of a possible regulatory pathway for a molecule with promise, in culture, for a rare spinal cord tumor; ultimately the progress to clinical trials happened more quickly than expected.
- By a partnership in which sometime competitors Celgene and Genentech are pooling their data to search for cellular markers, there is hope that new treatment could be available for follicular lymphoma in perhaps two years instead of ten.

**Scott J. Weir, PharmD, PhD (Institute for Advancing Medical Innovation [IAMI], University of Kansas)** explained that over the previous five years, the IAMI has collaborated with companies, PGs, and government to advance 10 new treatments to clinical trials. As an example, he described the Sarcoma Learning Collaborative (SLC), a partnership of IAMI, NCATS, and Children’s Mercy Hospital working to identify individuals and small groups – “citizen scientists” — who have passion and some resources, and want to have an impact on some of the 80 different sarcomas with approximately 24,000 new patients diagnosed each year. Two years after its formation, the SLC has six drug repurposing and drug projects running. The hope of the SLC is to make innovative models publicly available that may help identify both new individual agents and new combinations that could help to treat sarcomas.

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### Session III: Rules of Engagement

In PGCT stakeholder survey and interviews, the perceived potential for regulatory and legal problems, as well as the difficulty of managing conflicts-of-interest, was frequently identified as a barrier to PG engagement. The objective of Session III was to understand the key considerations in these areas.

A major focus of the session was the imperative that sponsor communications about investigational drugs, whether targeted to PGs or directly to patients, must be distinguishable from promotional materials. Speakers representing both Industry — **Carla Cartwright, Global Regulatory Policy & Intelligence Johnson & Johnson**, and the FDA — **Richard M. Klein, FDA Office of Health and Constituent Affairs**, spoke to the guidance for Promotion of Investigational Drugs (see 21CFR § 312.7), explaining that simply put, the guideline states that it is against the law to represent in a commercial context (that is, an advertisement) any *suggested, implied, or explicit* claims of safety and efficacy for a use for which a drug is under investigation.

Attendees were told that clinical trial recruitment ads (CTRAs) represent the beginning of informed consent. As such, CTRAs must include all of the elements of informed consent in language that patients can understand, including potential risks and benefits of being in the trial including a statement that there may be

unknown risks. If applicable, there must be a statement that patients who enroll may be randomized to treatment with placebo, and the term “placebo” must be defined. The same restrictions apply to ads targeted to PGs, and furthermore, such ads cannot imply that trials are a good way to get treatment for a patient who cannot afford it.

In general, companies should not mention the investigational product by name, and so the CTRA includes very basic information, such as the contact information for the clinical investigator, the condition under study, a summary of eligibility criteria, such benefits as exams or medications at no cost, and the time and travel commitments.

Mr. Klein summarized the regulations specific to research patient recruitment:

- Any communications intended for patients must clearly characterize the trial as research, and should never imply that the study offers treatment.
- Communications about a clinical trial should never characterize the investigational product(s) as either safe or effective.
- Sponsors and PGs informing a patient or PGs about a trial must adhere to IRB-approved materials.

The speakers pointed to innovative ways that companies are able to offer trial-specific information, with confidence that they are not at risk from a regulatory/legal standpoint. Examples include apps such as The Michael J. Fox Foundation’s Fox Trial Finder, with patients able to enter their zip code and some medical and family information, and potentially be matched up with a clinical trial. The FDA/NIH website [clinicaltrials.gov](http://clinicaltrials.gov) prominently highlights that the trial information that sponsors post there is “For Patients & Families,” in addition to researchers and others in the clinical trial space. The FDA is piloting a program called Drug Trials Snapshots, which will provide the public with access to demographic characteristics of participants in the clinical trials of recently approved drugs, as well as study design, efficacy and safety results ([FDA Drug Trials Snapshot pilot, accessed 01 February 2015](#)).

**Ronald J. Bartek, President, Friedreich’s Ataxia Research Alliance** focused on potential COIs, both real and apparent, between PGs and Industry partners. Everything the PG is able to accomplish and all the assets it is able to provide to its partners — fundraising, grant making, patient registries, natural history databases, bio-repositories, cell models, recruitment — depend on having the trust of its constituent patients, families, and donors. PGs must always be seeking deeper relationships with Industry and Academic partners, almost always involving financial engagements, which are both legal and ethical. Disclosure and transparency of such relationships are key for the PG to build and maintain their constituents’ trust.

PGs can manage potential internal COIs— involving the PG’s own officers, staff, or board of directors – through informal monitoring by entities such as the Better Business Bureau (BBB) Center for Science in the Public Interest, or Charity

Navigator. The BBB Center maintains that a charity should engage in no transactions in which any board or staff members have material conflicting interests. On request by a PG, Charity Navigator will monitor and rate the PG's transparency and management of COI, and will make the rating publicly available.

External COIs, involving the PG's relationships with Industry and Academic partners, the FDA, and other PGs can be more difficult to navigate. There are sparse government guidelines from the Department of Treasury and the FDA that can be applied to PG partnerships with Industry or Academic sponsors.

When the flow of capital is from Industry to the PG, managing COI requires transparency and full disclosure to maintain patient trust. If the PG is an IRS-recognized charity, then IRS requirements apply as well. Transparency, full disclosure, and the PG's independence must be ensured when the flow of capital is from the PG to sponsors, such as when PGs provide matchmaking between a small biotech with a promising compound and larger pharma companies who can take the compound to clinic; provide Industry partners with access to natural history databases and registries for recruitment; provide their networks of clinical sites where trials can be conducted; or fund Industry through research grants and investment capital.

The FDA is not concerned about potential COI when a PG representative accompanies an Industry sponsor to a pre-IND or milestone meeting. On such occasions, he said, it is clear that the PG is there in support of the sponsor's case. However, what the FDA does *not* want is for a key person from the PG, such as a staff member, officer, or director to serve as the advisory committee's patient representative, if the PG is significantly engaged with the sponsor.

PGs may legally and ethically make Program Related Investments (PRIs), supporting Industry partners with the purchase of stock or with loans, granted the primary purpose of the investment is to promote the PG's charitable objectives; and the existence of a high potential rate of ROI does not in itself prevent the PG's investment from qualifying as a PRI. Mr. Bartek observed that in his experience, PGs have very little input on drug pricing, other than appealing to Industry to be mindful of the contributions that their patients have made in helping the company get to market. However, PGs often do help companies make the case for unmet need in talks to payers about reimbursement.

**Rebecca Prince, Sr. Corporate Counsel Bristol-Myers Squibb** spoke to the rules of PG engagement from the perspective of in-house counsel, whose role is to assess legal risks and help structure the company's potential interactions, for example, with PGs, in a way that mitigates risks and removes barriers. If the company is engaging with a PG to access the PG's tangible resources, such as patient registries and databases, or a network for real time patient communication, then both the arrangement and the potential risks to the company will be different than if the company is engaging with a PG because of its KOLs and expertise in patient education and recruiting. When the PG is to be a service provider to the

company on a contractual basis, the relationship should be discussed in detail, so that there will be no confusion about roles and responsibilities. When the company is engaged with charitable giving to a PG, either with a donation of funds to a 501(c)(3) non profit, or by Corporate Sponsorship for general or specific education projects, then to mitigate risk, the donation must be unrestricted, and the PG must have independence.

## Session IV Breakout Groups

Attendees were each assigned to attend two of three possible breakout groups for more in-depth and interactive discussion. Breakout assignment was designed to result in a roughly equal proportion of PG, Industry, and Academic representatives participating in each breakout session.

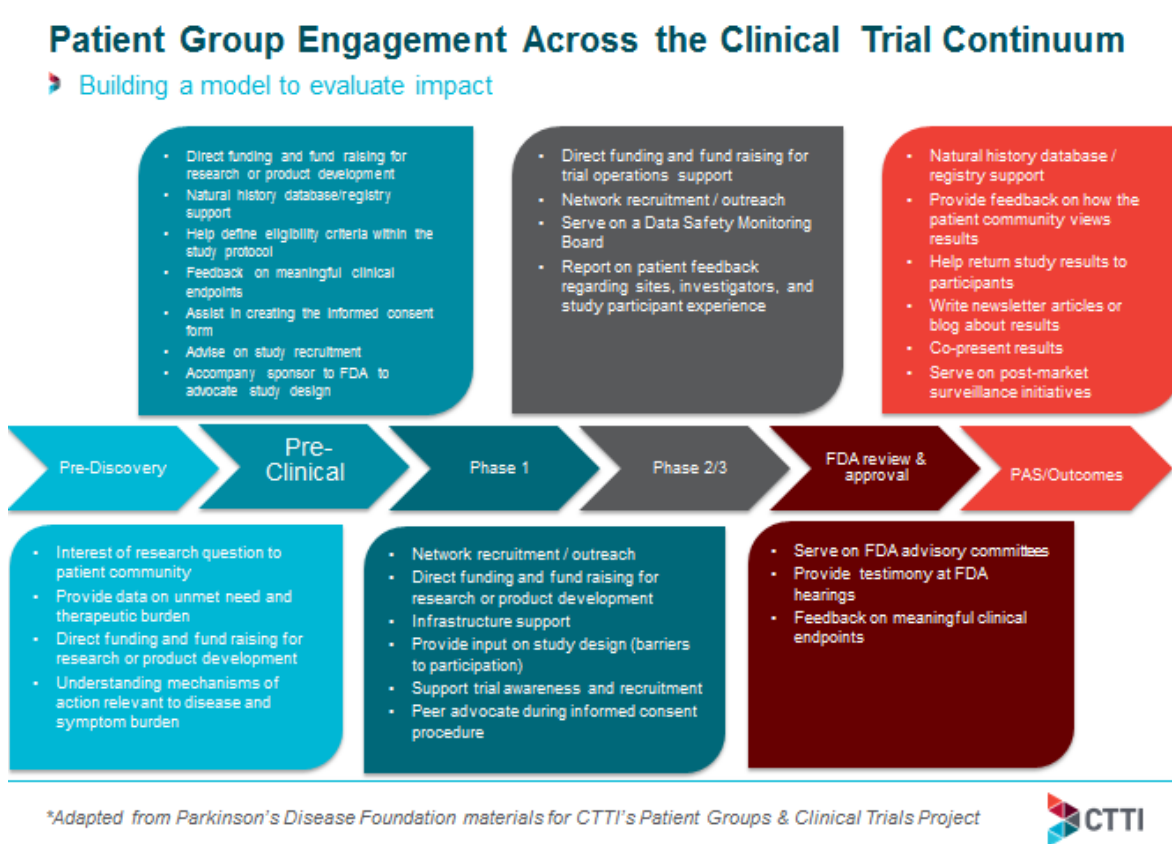


Figure 1: Patient Group Engagement Across the Clinical Trial Continuum

Breakout 1 participants discussed the ways in which PGs should assess Industry and Academic sponsors as potential partners. They reported that, to make the discussion broad and inclusive, they chose to think of partnerships between PGs and *any* sponsor, not only Industry. Dr. Joel Beetsch reported that the group

learned in breakout that it was more often the case that the sponsor first approached the PGs with a request to partner in some way, rather than PGs approaching the sponsors. Participants discussed ways in which PGs might reverse that, by assessing what they could bring to the sponsor and then reaching out to a sponsor with a proposal.

**Breakout 1** reported devising a list of very basic principles that can be used to guide PG and sponsor partnerships:

- **Company and patient-focused designs must be aligned.** Sometimes there is a lot of contact up front, then the initial people leave the sponsor, and the PG needs to start over
- **Know how long the relationship will last.** Does sponsor have the resources and focus to sustain the partnership for the long term?
- **Try to limit the points of contact** in the company to as few individuals as possible, to have a consistent understanding.
- **Make sure both sides understand what each hopes to gain.** A corollary to this was, when a particular PG is working with multiple companies, the group should not pit one company against another.
- **Don't divide the patient community.** To help patients, we need expertise from all sides – think in terms of complementing skills, not competitive ones.
- **There should not be an expectation that the PG has loyalty to a single company or a single product.**
- **Sustainability can mean long or short-term, provided both parties understand.**

In Breakout 1, participants came up with a list of fundamental questions that PGs should consider asking of sponsors who wish to partner with them:

1. Why have you chosen to partner with us?
2. Are you working with other groups?
3. What are your long-term and short-term goals in this field of research?
4. Do you have an organizational structure that supports engagement, and how are those staff trained?
5. What will be the roles and responsibilities of each partner, between the PG and the sponsor?
6. How often, with whom, and what content will we communicate? This has to cover general communications, issues of intellectual property and confidentiality agreements.
7. What will be expected of the PG?
8. What will be our interactions in the competitive space – how will confidentiality be handled?
9. Is the sponsor willing to financially support activities that require staff time of the PG?

10. What is your involvement with extended access programs? PGs are very helpful as to where the patients are, particularly in rare diseases.
11. How have you been involved in this disease in the past; will you be involved in the future?
12. Are you open to suggestions about how our relationship will be structured, and how the scope of work should look?

Breakout 1 participants urged partners to take their time in assessing a new partnership, to document the agreements, and to consider having an MOU or a more formal contract. They also felt that one gap was the lack of some sort of guidance document, which PGs and regulatory agents could assemble to outline some of this work. Safe harbor guidance would be very helpful.

**Breakout 2** participants reported that they had changed the focus of their discussion, from how Industry and Academic sponsors should assess the assets of PGs, to what do PGs need to know and understand about their assets, and the worth of them, before the PG discusses partnering with a sponsor? What evidence does the PG need to demonstrate their assets?

Breakout 2 participants saw the CTTI infographic on patient group engagement in the clinical trial continuum [Figure 1] as a tool to analyze PG strengths and gaps, assigning different PG skills and strengths to different phases of drug development with the greatest relevance. To demonstrate to sponsors how they can help, PGs could use the *continuum as a template* to help define their values and document their assets depending on the needs of the partnership.

Breakout 2 participants listed the following assets that PGs could bring to the table to enhance the CTE:

- PGs can provide patient-driven risk/benefit analyses
- PGs can participate in FDA meetings
- PGs can display the extent of their outreach and networks
- PGs can provide funding for correlative studies
- PGs can create buy-in with the patient community

Breakout 2 also reported some precautions that PGs should take when preparing to engage with sponsors:

- PGs should have an independent evaluation of a potential partner's science before they invest.
- PGs should not sign exclusivity agreements for use of their assets. Openness and transparency should be bilateral, and required of the sponsor as well as of the PG.
- PGs must actively manage their relationships and maintain their autonomy: Especially if the PG is the funder, don't be afraid to create accountability and milestones, and don't be afraid to say no to a partnership. The example



was, if a sponsor is only seeking to engage the PG because the trial needs rescue, the PG may not want that partnership, as opposed to one in which the PG would have input early in development.

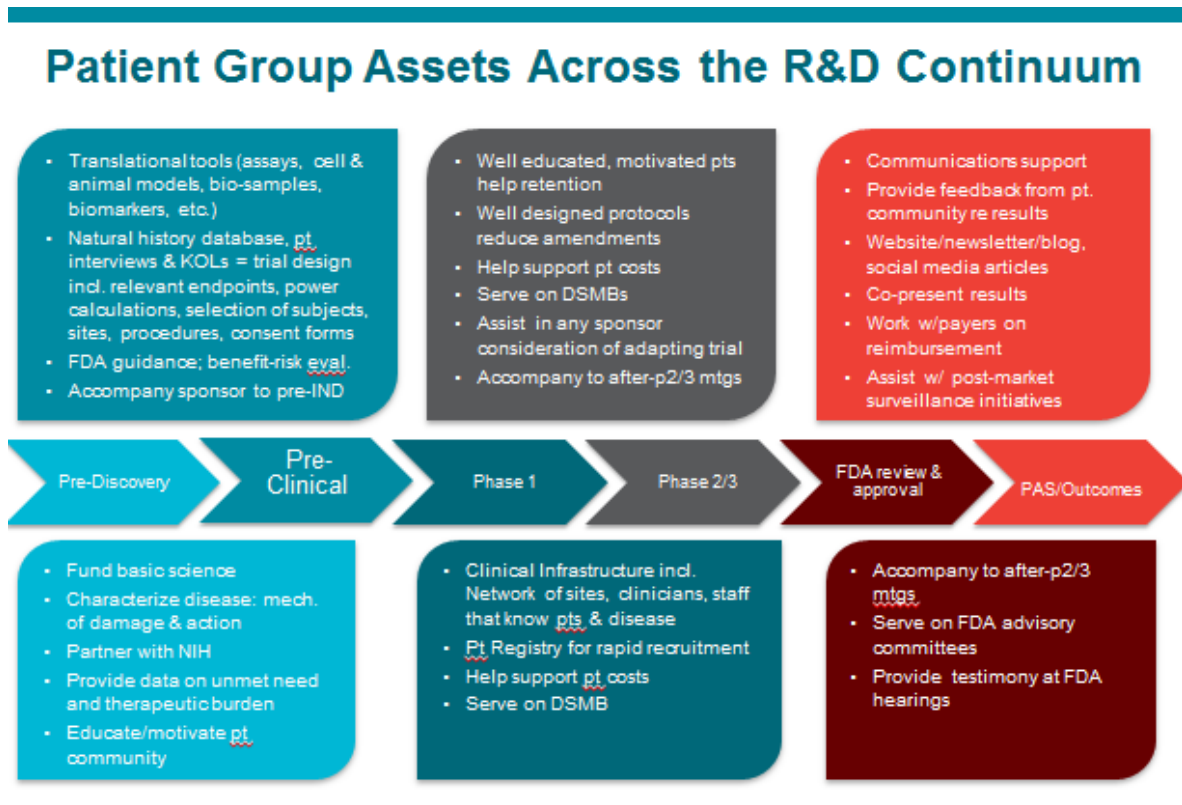


Figure 2: Patient Group Assets Across the R&D Continuum

In **Breakout 3**, participants discussed ways to understand “value” in terms of PG effects on variables throughout the clinical trial continuum, and what metrics are appropriate to measure such value. There was acceptance that, in talking about the value proposition of PG engagement, the focus should be in terms that are meaningful to the entire CTE, but particularly to patients. It needs to be acknowledged, in trying to determine value metrics, that the *stakeholders all have different incentives, funding structures and accountability.*

Breakout 3 participants arrived at pertinent questions around values and metrics, as follows:

**What are the next elements of data needed for Industry and the FDA to move forward with greater PG engagement?** If there were a graph that showed what money has to be invested to have PG engagement, and what benefits come out, such as shorter time to market, or greater patient acceptance, and better

outcomes? But PGs represent a broad spectrum of organizations of all sizes, with varying assets and abilities, so that predicting value is not one-size-fits-all.

Breakout 3 participants returned repeatedly to the **clinical trial continuum**, in order to talk about the main phases and time points where PGs could have impact.

**How is value defined?** In Breakout 3, there were many opinions on this point. It was noted that value needs to take into account currently available treatments, as well as possible new treatments, because if current treatments are safe and effective, there is less to be gained with new treatments, or “me-too” drugs. Traditional metrics, such as recruitment and retention, or study adherence can be weighted in terms of effect on cycle time. The Breakout 3 participants noted that CTTI’s work is trying to define those metrics and also to include the cost of delays and amendments.

- Value is defined by benefit to the patient group if the disease is one of the 10% that have an identified treatment aligned as an indication; value can be quantified if PG assets and influence have moved the needle to bridging an unmet need or furthering the pipeline.
- Value to the Industry sponsor for patient group engagement is primarily around recruitment/retention engagement as the business model is still working on best practices around the value proposition, as the primary focus is on recruitment, retention, delays, amendments, time to market, and overall market ROI.
- The categories of risk, cost, revenue, time and intangibles were not universal terms of understanding and there was consensus that additional work needed to be done to have a translatable conceptual model move the value propositions forward from all stakeholder perspectives.

**What should be measured to make the value proposition for PG engagement?** The one area where consensus was reached easily was that no one was in favor of measuring ROI. There was discussion around stakeholder sensitivity to talking of PG engagement in terms of profit versus partnership.

- PROs (Patient Reported Outcomes) were also universally accepted in theory, but their inclusion into the clinical trial process and regular healthcare delivery has been minimal.
  - PGs and industry partnerships have been called out to help highlight treatment efficacy and symptom burden relief, but there is a lot of work to do with “new” endpoints in trials, and who pays for the validation work.
- Improved QbD (Quality by Design) with PG input on protocol design which hopefully will lead to better adherence/retention, recruitment, and targeted alignment with the true disease burden.
- Risk tolerance variation for patient groups to add to FDA decision making as well as industry design of new drugs in areas of unmet need.
- Effects of Natural History studies and longitudinal data held by Patient

groups as a living repository of the disease state.

**What are the tools available or need developed to illustrate the value of patient group engagement?** One suggestion was to look at the benefit/risk ratio, and determining the risk tolerance in a given disease, based on patient preference studies that could enhance the probability of regulatory success. There was also discussion about how to evaluate trial burden at the site, patient, and operations levels.

- Trial network development: HOW-Tos on contracting and IRB oversight, standardized resourcing, how best to resource trial operations
- FDA – PDUFA VI / PFDD / Ecosystem accountability to patient groups stratified to additional disease states outside of current roadmap
- Culture stress testing – Paradigm shift of Patient centered accountability (MD training has not been patient centric), subjective vs. objective measurements,
- Guidance docs have high impact, what about review division training
- PRO empowerment – funding and methodologists needed
- NASH equilibrium analogy – (standard endpoints vs. innovative endpoints)
  - Who moves first in regulatory game: strategy - guidance
- Publications – peer reviewed – Add additional scientific validity to the field
- Benefit / Risk basis of understanding impact of Actual Treatments against a shifting disease burden

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## Session V: Value and Metrics

Session V was focused on the understanding of “value,” from the perspective of all stakeholders, in terms of PG effects on variables throughout the clinical trial continuum, and what types of metrics are appropriate to measure such value.

**Kenneth A. Getz MBA, Director for the Study of Drug Development, Tufts University School of Medicine**, made the case that the value of PG involvement can be measured in terms of avoiding the high cost of clinical trial delays.

In 2013, the cost of the drug development cycle, including lost opportunity costs and costs of failed drugs, was estimated at *\$2.6 billion, roughly 2.5-fold compared with only 10 years earlier*. A major factor in the increase has been clinical trial delay, based on evidence derived by financial modeling. In turn, much of the delay to study completion is due the complexity of clinical studies, which is much greater than it was 20 years ago based on studies in general having greater numbers of endpoints, eligibility criteria, procedures, visits, and more protocol amendments. As more complex trials increase the burden on sites and studies, *study enrollment times have nearly doubled* across all therapeutic areas.

Financial modeling suggests that even minor improvements either in trial speed or success represent high cost savings. Four major areas in which PG input and

patient-centric considerations could reduce delay, increase trial speed and efficiency, and increase success rates include the following:

- Improvements in feasibility, so that the protocol is simpler to administer and to complete for the patient
- Enhancing convenience, so that it is easier for patients to stay in the study
- Creating greater relevance – using patient community input to identify and study the highest priority unmet need
- Building patient ownership and commitment to the program's success

**David P. Leventhal, MBA, Director of Clinical Innovation, Pfizer Inc. Worldwide R&D**, spoke to Industry considerations in measuring the value of PG engagement in clinical trials. For a company like Pfizer to engage in patient-centric activities on the drug cycle overall from filing the IND to NDA approval would take system-wide, disruptive changes to how the clinical teams work, how the investigators conduct studies, and to the standard operating procedures of Finance, Legal, and Regulatory. To be compelling to the company's leaders, the value that PGs bring must outweigh the disruption both financially and operationally.

Pfizer has a framework of patient engagement initiatives at each stage of pre-study planning, recruitment, and post-trial. However, with the company running more than 400 clinical trials at any time, the demands of time, resources, and legal processes to accomplish system-wide PG engagement are daunting. As stakeholders talk about value metrics, the cycle time metrics are important, but the cost of changes must also be in the equation, and Industry needs the PGs' help to make those changes a reality.

**Bennett Levitan, MD PhD, Director of Epidemiology at Janssen/Johnson & Johnson** listed five drivers of pharmaceutical project value, including revenue, time, risk, intangibles, and strategic relevance. Risk takes many forms, for example technical risk of choosing to advance development or not after each study, regulatory risk of having the product approved or not, and forecasting risk, or whether the earnings are as much as planned.

Dr. Levitan demonstrated expected net present value (ENPV) modeling as a means to quantify impact of multiple value drivers collectively in a clear and accepted summary metric that can be *adopted to value PG engagement in clinical programs*. In ENPV modeling, the different possible ultimate outcomes — for example, success or failure of a drug development program — are each broken into stepwise events. The success of one event brings the opportunity to attempt the next event, as completing Phase 2 brings the opportunity to attempt Phase 3. Each stepwise event can be assigned a probability of success and of failure based on the company's data such as benchmarks achieved or not; the company's drug development history; or PK/PD modeling. *ENPV modeling accommodates real-world complexity, such as a compound being developed for multiple indications, parallel development paths, or multiple regulatory agencies.*

Using examples of PGs assisting in recruitment, providing peer advocacy during informed consent, and participating in studies to select weighted study endpoints, the positive impacts of each PG activity were quantified on the basis of improving risk, revenue, or other drivers, collectively increasing the net present value (NPV) of successful regulatory approval.

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## **Progress through Partnership: Integrating Patient Groups into the NCATS Clinical Research Process**

Petra Kaufmann, MD MSC, serves as Director, Division of Clinical Innovation, NCATS, overseeing the Clinical and Translational Science Award (CTSA) program. She noted that translational research requires a multidisciplinary team made up of Industry, Academia, and patient advocacy to bring benefit to patients. The report of a recent Institute of Medicine (IOM) review of the CTSA program included seven high-level recommendations, the sixth one being that the CTSA “Ensure community engagement in all phases of research.” Dr. Kaufmann pointed out that it is critical that the clinical research community moves from seeing patients as consumers to seeing them as partners from the beginning, when they can ask, “Does this research question really matter?” or can make sure that the protocol is not too burdensome, and that the informed consent can be understood.

Dr. Kauffmann noted that partnerships with PGs must not be limited to Phase III, although the patient voice has a great impact on recruiting and study compliance. She gave the example of parents who allowed their healthy infants to participate in a trial, in order to help friends whose child had the disease under study.

Patient representation on the trial’s steering committee, and on the data and safety monitoring board (DSMB) can help the clinicians and statisticians understand the patient perspective, for example from a patient or family member who knows the disease first hand and who can say, “this or that AE doesn’t matter, when we are considering the only potential treatment available for an otherwise fatal disease.” Engagement at this level of a trial also helps the patients to understand how seriously the trial team treats the safety of patients.

Dr. Kaufmann listed some successful private-public partnerships at NCATS:

- Through the Rare Diseases Clinical Research Network (RDCRN), 22 distinct consortia engage more than 2500 investigators from multiple disciplines at 240 clinical sites in the US and 14 other countries. RDCRN consortia are working with almost 100 different PGs on clinical and natural history trials, to make faster progress toward treatment options for more than 200 rare diseases.
- The Coalition of Patient Advocacy Groups (CPAG) represents the perspective and interests of all PGs associated with the RDCRN. Patient groups that are members of CPAG have influence on the direction of the RDCRN as a whole, and not only in their particular disease area.
- NCATS’ program Discovering New Therapeutic Uses for Existing Molecules

(NTU) New Therapeutic Uses (NTU) provides a framework for companies and investigators to repurpose agents that did not go to market for reasons other than safety. NCATS provides the NTU framework; the Industry sponsor provides drug and pertinent data; and Academic researchers provide understanding of the disease, ideas for new concepts to test, and a connection to patients in need of new treatment options. Every research application to the NTU must include the plan for PG engagement.

In closing, Dr. Kauffmann said that NCATS is trying to demonstrate and disseminate successful models of stakeholder collaboration. Stakeholder partnerships with PGs are critical across the entire clinical trial continuum, and the process must be transformative, not small steps, because there are thousands of diseases and far too few treatments.

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## DISCUSSION

Repeatedly throughout the Expert Meeting, attendees echoed Dr. Janet Woodcock's conviction that the object of the PGs, and indeed of all the stakeholders in the CTE, is to build a stable of treatments for disease, so that people are no longer suffering. While all attendees concurred that many barriers remain to be addressed, there was also wide acceptance that Industry and Academic sponsors' engagement with PGs can improve design of clinical trials; improve adherence to clinical trials as well as to marketed drug regimens; help to identify appropriate patients for trials; accelerate research through the spread of trial information to patients; develop tools to capture and share PRO data across stakeholders, and spread education about the disease, drugs, and trials to patients and families as well as clinicians.

To that point, common themes heard in the formal presentations, interactive discussions, and the breakout sessions included the following:

- The patient voice is key to understanding the day-to-day effect of the disease, and the acceptable risk-benefit of treatment. Engaging PGs is a means for companies to understand patient and family needs so that companies can develop not only new treatments, but services that demonstrate a commitment to patients and their wellbeing, not only to drugs and revenue.
- Whereas talking with individual patients and focus groups has value, sponsors who form committed engagement with PGs have setup a formal intermediary to help them engage with potentially thousands of patients over many years.
- Regarding empowerment of individual patients, the groundswell from patient interaction through social media can be amazing, but those interactions by themselves do not lead to the kind of focused approach needed for PGs to interface collectively with Industry.
- There is critical need and tremendous value to having the patient

perspective in protocol design, and to seek patient-centric input into whether the trial as planned will be unduly burdensome. PGs can contribute to the feasibility of trial designs with their knowledge of the needs and limitations of patients in getting to trial sites or following the trial protocol. Providing feedback for trials that are more “fit for purpose”, “fit for patients”, will translate into increased trial success with minimal time and resources to allocate.

- PG’s disease-specific registries and data bases can particularly help to match patients with trials that may be appropriate for them in terms of their eligibility, geography, and ability to participate and follow the protocol. These are significant and most apparent for rare disease networks where patient groups have curated their disease state into the appropriate genotype and phenotype to be studied and meet unmet needs.
- When engaging with PGs, the company needs to know each group’s priorities and their past and present programs, their capacity, and their strengths, whether in influencing policy, funding research, or connecting with patients.
- Industry looks to PG to accelerate the regulatory process. PGs can provide to help companies with regulatory pathways, as when the Friends of Cancer Research wrote the regulatory process for breakthrough therapies.<sup>1</sup>
- Engagement of PGs with Industry, Government, and Academic stakeholders requires a unified and systematic, structured approach to identify the strategic priorities for collaborations and alignment of resources, essentially a roadmap for substantive patient group engagement. [Figure 1]
- While it is difficult to work out arrangements in which Industry competitors engage and share data and learnings, sponsors competing in the same disease spaces can see mutual benefit by coming together to engage with PGs. One example is the great need for Industry and PGs to work together to validate new PROs, which, although extremely costly, could be manageable if shared among the companies and different shareholders.
- Around the question of PGs supporting research as a form of venture philanthropy, some PG stakeholders noted that when they are funding trials or other development, the partners must recognize that there could be ROI, and should form a memorandum of understanding (MOU), defining the management, committees, how teams would be selected, management of intellectual property and revenue sharing. The idea is not just to distribute

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<sup>1</sup> A new drug may be designated as a breakthrough therapy by the FDA if it is intended to treat a serious or life-threatening disease and preliminary clinical evidence suggests it provides a substantial improvement over existing therapies. Once the breakthrough therapy designation is requested by the drug sponsor, the FDA and sponsor work together to determine the most efficient path forward. As of January 30, 2015, FDA has given 18 approvals to drugs designated as Breakthrough Therapies, 12 of them first time approvals for novel drugs ([Friends of Cancer Research, cited 31 January 2015.](#))

the PG's funds, but to return any earnings to funding further advocacy and research – an “evergreen” approach to investment.

- The individuals heading up the engagement for each of the partners makes a huge difference in the quality and outcomes of the partnership. It is critical that persons with energy and passion work out the best practices, and then document their experiences.

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## Conclusion and Next Steps

In closing the PGCT Expert Meeting, Bray Patrick-Lake expressed a sense that the presentations and conversations that took place validated a lot of the work that the PCGT team had been engaged in to date. She explained that the Expert Meeting was a jumping off point; that the attendees will be considered contributors to the fabric of the project, and their input in this meeting will be used to shape the PCGT team's recommendations document on optimizing partnership with PGs around clinical trials.

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## FUNDING STATEMENT

Financial support for this project is provided by grant #1R18FD005292 from the Food and Drug Administration (FDA) and CTTI membership fees.

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## ABOUT CTTI

The Clinical Trials Transformation Initiative (CTTI) is a public-private partnership to identify and promote practices that will increase the quality and efficiency of clinical trials. The CTTI vision is a high quality clinical trial system that is patient- centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.

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