CTTI RECOMMENDATIONS:
EFFECTIVE ENGAGEMENT WITH PATIENT GROUPS AROUND CLINICAL TRIALS

Part I. Background

With the increasing commitment to Patient-Focused Drug Development (PFDD) by FDA and patient engagement in translational research, there is a significant opportunity to improve the clinical trials enterprise and enhance participation by patient groups in the work of trial sponsors. The term PFDD, as used here in the broader sense, refers to the meaningful engagement of patients in the development of therapeutic products, and the various important roles patients can play in improving the entire enterprise, from study endpoint selection that reflects outcomes meaningful to patients, to recruitment and retention in clinical trials, and more effective postmarketing safety. Yet clarity is needed about 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. Also lacking are metrics by which the value of such engagement, in terms of regulatory and market success, might be measured. After decades of emphasis on mechanisms to speed “bench to bedside” development, PFDD and patient engagement in research should be considered an effort to extend the benefits of incorporating patient insight and experiences, as well as desires and preferences, from bench to bedside and back.

Throughout this CTTI project, we use the term “Patient Group” (hereafter PG) to encompass patient advocacy organizations, disease advocacy organizations, voluntary health agencies, nonprofit research foundations, and public health organizations. Note that for clarity of focus, our use of the term PGs is not meant to refer to individual patients or advocates, although PGs may engage patients/advocates for clinical trial activities with sponsors of research. Further, these recommendations are intended to enhance the quality, frequency, and collaborative nature of partnerships between sponsors of research and PGs throughout the research and development continuum. These collaborations will enhance the “voice of the patient” in all aspects of the clinical development process.

As part of the data collection for this CTTI project, a qualitative scientist conducted 32 semi-structured interviews with 10 leaders of PGs, 12 industry sponsors, and 10 academic investigators following a joint CTTI/Drug Information Association (DIA) survey. The survey elicited feedback from 244 respondents and examined current practices and perceptions among the 3 stakeholder groups about the value of, and barriers to, successful PG engagement in clinical trials. Results from the survey showed that PGs identified engagement with research partners as having greater benefit for partners than was reflected in the responses of the academic and industry partners themselves. Several explanations may exist for these disparate perceptions, including a lack of incentives, training, and resources for research sponsors to encourage this type of engagement throughout the drug development process.

Presentations and discussions during the January 2015 Expert Meeting also suggested that this disparity may be due in part to differences in therapy development between common and rare diseases. It may be that, rather than seeing a need to partner with PGs, research sponsors working in common diseases have believed to date that they could rely on the huge infrastructure and many decades of experience in their common diseases to provide the required assets for their clinical trial enterprise (e.g., therapeutic targets, animal and cell models,
natural history, protocol design, clinical endpoints, access to patients). However, as more precisely defined genetic diagnoses within some common diseases continue to result in numerous subpopulations that constitute multiple rare diseases, PGs representing these subpopulations may be called on to partner with academia and industry in much the same way as is currently done in rare diseases.

Results from the CTTI/DIA survey, semi-structured interviews, and Expert Meeting\(^2,3\) have led to a better understanding of the diverse capabilities and assets that many PGs are assembling in order to develop valuable services and enhance their active engagement in the clinical trials enterprise. The Expert Meeting also provided an opportunity to consider multiple examples of how and when research sponsors are engaging PGs to build effective partnerships. While few PGs offer the full complement of expertise and assets, many provide a good number of them and are eager to develop more.

Throughout the recommendations described below, we characterize the range of “best practices” that respondents report are producing positive results. We hope these serve as guideposts for PGs and research sponsors alike.

**Part II-A. Recommendations for All Stakeholders**

1. **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 patients’ voice) in the early stages of disease targeting, making full use of PG input while clinical trials are still in the planning phase to help shape and refine the study protocol [Figure and Tool 1]. Soliciting PG input early in development benefits both sponsors and patients. Sponsors benefit by a clearer, more focused understanding of unmet need, therapeutic burden, opportunities for expanding indications, and better targets; by improved clinical trial design, selection of optimum subjects, endpoints, and clinical sites; by faster trial recruitment and greater patient compliance with the protocol; and by alleviating the need for costly and time-consuming adjustments later. Patients benefit by less burdensome study protocols and more meaningful and relevant endpoints, thus increasing the likelihood they will participate in the trials and potentially help to develop a meaningful treatment for their disease.

2. **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.**

   PGs and research sponsors often have different backgrounds and perceptions of the value that patient representatives bring to the trial, or the tasks that PGs will be expected to undertake. At the outset of the development program, it is important to clearly delineate the roles of partnership and clarify the goals and objectives of the collaboration. Responsibilities and expectations should be outlined in agreements reflecting the resources being committed, data being shared, or overall nature of the program (e.g., early vs. late phase, trial process issues, informed consent forms, patient-reported outcomes vs. clinical endpoints).
While 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. These multiple influences reflect the reality of the environment that will drive the program, and PGs should understand that research sponsors reserve the right to make final decisions about study design. However, decision making may shift to, or be shared with, a PG if they have funded the study or have invited the sponsor to participate in their development program. Expectations about the role of PG consultation and input should be clarified at the start of the collaboration. The scope of work for each entity can be clearly defined through a simple Memorandum of Understanding (MOU) or brief contract.

3. **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. Commitments between partners should be prespecified and documented in an agreement, including how teams will be formed and intellectual property and revenue sharing will be managed. Documentation should be customized to fit the needs of each partnership and may include an MOU or more formal contract.

Much of drug development is a commercial activity, and as such needs to protect commercial and confidential information and other trade secrets in order to safeguard the intellectual property and investments by sponsors. However, stakeholders should be open and transparent to the degree possible to facilitate informed and educated input and collaboration between sponsors and PGs. Confidentiality Agreements (CAs) and Non-Disclosure Agreements (NDAs) allow sharing of sensitive information with PGs for this purpose. PGs must abide by CAs and NDAs they sign with sponsors to enable open communication. Similarly, PGs have confidential information they may wish to protect and sponsors should abide by NDAs signed with PGs.

4. **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 and thereby increase the chances that one or more of these therapies will succeed. Likewise, 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.

5. **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. In fact, as demonstrated by Janet Woodcock’s statements at the Expert Meeting, the FDA encourages engagement as a means of facilitating clinical trial design, awareness, and enrollment. There are a number of FDA-related and other legal issues surrounding PG engagement. 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. PGs may contribute to clinical trial design and assist with trial recruitment (e.g., raising awareness, assisting with screening). In doing so, it is important for the sponsor and the PG to clearly characterize these studies as research. The studies should not misrepresent the investigational nature of the trial, explicitly or implicitly. To avoid misinterpretation in advertising a clinical trial, sponsors and PGs should convey the information about the trial as approved by the Institutional Review Board (IRB).

Each type of PG engagement will have its own contractual rules and parameters to mitigate risk. While there are many different models, the following are some common examples:

- PGs as service providers to the company on a contractual basis. The relationship should be discussed in detail so there is no confusion about the terms of the contract (i.e., roles and responsibilities). If the sponsor is retaining the PG to do certain work with a tangible end-product, the PG should be compensated fair market value.
- PGs as recipients of charitable giving from the company, either with a donation of funds to a 501(c)(3) nonprofit or by corporate sponsorship for general or specific education projects. To mitigate risk, the donation must be unrestricted and the PG must have independence.
- PGs as non-compensated collaborators.

To avoid actual or perceived improper influence by PGs, research sponsors should proactively establish their own rules of engagement. In any type of PG engagement, an NDA may be appropriate depending on the level of disclosure of commercial, confidential, or trade-secret information to the PG. It is important for research sponsors to understand their institution’s legal, regulatory, and research administration requirements before engaging with PGs. Before selecting a type of PG engagement, research sponsors should evaluate the legal risk related to confidentiality, privacy, kickbacks, promotion, appearance of conflict, and recognition of when informed consent begins. Generally, legal and regulatory counsel, preferably those familiar with PG engagement, should review plans, to ensure that appropriate, but not overly conservative, measures are taken. PGs engaged with research sponsors should be sensitive to these legal considerations and should honor requests by the sponsors regarding confidentiality and how they should communicate about their clinical trials.
Part II-B. Recommendations for Research Sponsors—Industry and Academia

1. Integrate into your ongoing research and portfolio planning an assessment of PG expertise, assets, and value to your program.

For industry research sponsors, the primary drivers for PG engagement are achievement of project milestones, corporate culture, and therapeutic area/vertical business unit interaction. However, these drivers are not always aligned with the project teams responsible for development of clinical programs. The barrier to PG engagement cited most often is internal resistance and lack of buy-in. Research sponsors should plan to build awareness within the company about the impact of PG engagement on clinical drug development. Awareness will help minimize resistance, provide examples of successful PG impact, and offer a platform for understanding how engagement aligns with the goals of both the clinical program and the company. Establishment of this platform will ensure appropriate support at multiple levels in the company and provide a mechanism for keeping staff current with best practices and metrics around PG engagement.

Research sponsors need to develop and execute a comprehensive roadmap for substantive PG engagement. These plans should encompass early Research and Development (R&D) through later stage clinical development. Fragmented relationships and unstructured PG engagement can cause confusion, redundancy, and tax valuable resources. R&D, clinical, translational, and commercial/marketing divisions should align and coordinate to ensure clear roles and purposes in their interactions with PGs, especially when multiple divisions are reaching out to PGs. Research sponsors should consider identifying a single point of contact from the company or institution who has a sufficiently broad view of the internal dynamics of the organization as well as decision-making authority to enter into PG collaborations that can advance clinical development activities and clinical trials (see 4 below).
Last, it will be critical to achieve appropriate resourcing to support PG engagement. Specific and dedicated funding for PG activities should be prospectively built into clinical development programs, study budgets, and corporate support mechanisms to ensure timely, productive, and continuous engagement with the PG.

2. **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. Ideally, sponsors should select PGs that have excellent relationships with patients and families and who have worked with disease natural history registries, biobanks, trial networks, trial design, trial awareness and recruitment, dissemination of results, and broad communication platforms (e.g., electronic communication tools and forums). Sponsors should establish principles and processes to support nascent groups that are developing their assets and patient base.

Currently there are no industry-wide tools used to select a PG. This gap was identified in the interview process and Expert Meeting. CTTI has developed an infographic [Figure] and accompanying tool [Tool 1] on PG engagement across the research and development continuum that can be used to analyze PG skills and strengths, assigning those to different phases of drug development having the greatest relevance. To demonstrate how sponsors can help, PGs could use the infographic and tool as a template to help define their values and document their assets, depending on the needs of the partnership.

Additionally, it is imperative to assess PG expertise, interests, organizational capacity, and relationships [Tools 1–3]. When engaging with a PG, the sponsor needs to know about the PG’s priorities, past and present programs, and strengths in policy, finance, and research. Performing such an assessment can help the sponsor gain a comprehensive understanding of a PG before engagement.

Further, research sponsors should match assigned tasks to the group’s strengths. For example, a PG may not be able to influence public policies, but could effectively provide input into trial design or support building awareness about the trial. It is also important to recognize that some PG representatives may have either competing priorities or a personal connection to the condition (via family caregiving or illness) that may limit their availability to perform the task. Research sponsors should encourage growth and support the needs of PGs without driving the agenda. Sponsors can connect PGs with experts who support their engagement in research activities.

3. **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. Engagement with PGs should involve a discrete division of labor in which each group contributes its unique area of expertise.

Partnerships with PGs must not be limited to phase III of the trial. The learning acquired through preclinical engagement and during phases I and II should be incorporated into the
phase III protocol design and execution, leading to a greater impact on recruitment and study compliance.

Patient representation on the study’s steering committee and Data and Safety Monitoring Board (DSMB) can help clinicians and statisticians understand the patient perspective. For example, it can be invaluable when a patient or family member who knows the disease firsthand can say, “This adverse event doesn’t matter when you consider it’s the only potential treatment available for a fatal disease.” Engagement at this level also helps patients understand how seriously the trial team treats the safety of patients and how meaningful the patient’s contribution can be to the successful execution of a clinical trial.

The patient voice as communicated by PGs is key to understanding the day-to-day effects of the condition and the acceptable benefit-risk tradeoff of treatment. The FDA appropriately places a high priority on minimizing risk to trial participants, but PGs can speak to and provide data on the high risk to patients of living with the condition and, therefore, the risks patients are willing to take to test truly promising therapies. Engaging PGs is a means for research sponsors to understand patient and family needs so that sponsors can develop not only new treatments but also services that demonstrate a commitment to the well-being of patients.

Patients as Partners

At the CTTI Patient Groups & Clinical Trials Expert Meeting Janet Woodcock of the FDA stated that it is critical for the clinical research community to recognize the shift from “patients as consumers” to “patients as partners.” Researchers have succeeded when they consider such questions as, Does this research question really matter? Can we make sure the protocol is not too burdensome? Can the informed consent form be understood?

4. 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. Having a standard work practice will assist the sponsor in ensuring that all elements of the collaborative partnership are met on each project and will provide a means of measuring the success of that partnership. Elements of the work practice may include a database of previous collaborations, required documents, and clear lines of communication, which could:

- Support the integration of PG engagement into clinical program strategies
- Minimize any perceived burden to incorporating patient perspectives as part of this collaboration
- Ensure consistency across the clinical teams on the approach to and evolution of the work with PGs
- Identify parties responsible for relations with PGs if there are multiple people making contact with them
- Drive transparent communication between the research sponsor and PG
- Define and implement contracting and communication plans
5. 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. As standards across industry are evolving, it is important that sponsors and PGs agree on critical elements of measurement for each arrangement. Predefine what a successful engagement consists of and ensure there is alignment prior to embarking on the partnership.

A regular assessment of satisfaction related to objectives, expectations, and success of strategies is recommended. Some metrics reported in the CTTI/DIA survey assessed reduction in protocol amendments and recruitment times, increased retention rates, shorter cycle times, and more patent life during product marketing. Additional measures were related to the development and validation of endpoints and patient-reported outcomes.

Case Example 1
A company sought the input of Friedreich’s Ataxia Research Alliance’s key opinion leaders and others and consulted FARA’s natural history database when 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 3 of FARA’s 12 partner sites in only a few hours.

Case Example 2
Patient and caregiver experience can provide valuable input into protocol development to increase the chances of trial success. The Foundation for Prader-Willi Research attended a sponsor meeting to review a protocol for a regulatory trial. FPWR noted the protocol had exclusion criteria, which listed medications that caregivers reported were commonly used by their children in the age range targeted for the study. FPWR then worked with the sponsor to change the protocol and modify the exclusion criteria, which otherwise would have significantly limited the trial’s ability to recruit patients and potentially introduced delays into the timeline.

6. Establish ongoing relationships with PGs and communicate openly with them on a regular basis.

In addition to involving PGs early, study teams should communicate with them regularly throughout in the development program. Research sponsors should let PGs know how their feedback has been incorporated into the program. And, sponsors should acknowledge that the collaboration provides an opportunity for mutual education of both partners.

It is also important to maintain regular communication with PGs even when there is no study news. Communication about enrollment rates, presentations, publications, and results is highly recommended. It is also crucial to maintain a high level of transparency as agreed upon in NDAs or MOUs. Important study events, study modifications or cancellations, or redirection of research priorities should be communicated in a timely manner.
Part II-C. Recommendations for Patient Groups

1. **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. Therapy development is a team endeavor. The foundation of partnerships is the trust you have established with your patient community, families, and the clinicians who care for them. An important takeaway from our evidence gathering is the recognition that the trust placed in PGs by patients is second only to that given to physicians. 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. Also, be conscientious about your relationships with other PGs or umbrella PGs with related missions.

   Take advantage of opportunities to educate your partners about your disease area and provide the “connective tissue” among partners by:
   
   - Involving partners in workshops and meetings to advance the science and collaboration
   - Matchmaking among different partners such as academic investigators and government programs or industry partners and academic investigators
   - Making presentations or “grand rounds” to industry, government, and academic partners
   - Serving on advisory councils, steering committees, or external oversight boards at NIH, FDA, industry, and academia
   - Conducting periodic state-of-the-science meetings with FDA and, where appropriate, accompanying research sponsors to FDA meetings focused on priority areas of drug development

2. **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 articulates their value proposition. They also should strive to understand the economics of drug development and clinical research, as well as the associated regulatory and contracting processes. PGs can accrue important clinical trial assets sought by industry and academic partners, including:
   
   - A group of educated advocates
   - A base of knowledge and understanding of the disease mechanisms and natural history
   - Financial and organizational support for the basic and discovery science needed to develop the field
   - Development of, and access to, the translational tools required to advance discoveries to clinic (assays, cell and animal models, biorepositories, tissue and organ banks, biomarkers)
   - Patient preference or benefit-risk assessments
   - The clinical infrastructure needed for effective clinical trials (patient registries, natural history databases, clinical sites with clinicians and staff familiar with the disease and patients)
• A willingness and ability to assemble key opinion leaders, patients/advocates familiar with the disease, translational tools, and clinical infrastructure to assist in trial design that includes the selection of optimum subjects, endpoints, trial procedures, and clinical sites

Through active, continuous engagement in the development program, PGs can demonstrate a unique value to their academic and industry partners. This value has the effect of:

• Derisking early-stage development with funding and public-private partnerships for basic, translational, and early clinical research
• Reducing uncertainty in the regulatory process by working closely with the regulators throughout the entire R&D process
• Helping to develop more effective, efficient trials with a greater chance of success through better questions and study design, efficient recruitment, improved retention, fewer amendments, procedures that are better-suited to the patient, clinical endpoints that are well-grounded in the natural history of the disease, potential benefits that are most important to the patient, and the use of statistical plans powered to appropriately demonstrate safety and efficacy

3. 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 postmarket period [Figure and Tool 1]. Active engagement involves sharing the PG’s assets:

• When research targets and therapeutic pathways are being selected
• When tools (assays, cell and animal models, biosamples) are needed
• When financial support is necessary and potentially available from PGs
• By bringing patients together with research sponsors because such interaction can be motivational
• By taking an active part not only in conferences and forums focusing on the science of their disease, but also in discussions on drug development and regulatory policy matters
• By seeking out key thought leaders in academia and industry to build knowledge-exchange relationships well before a clinical development path is set

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.

PG engagement could involve the following activities.

**During the prediscovery phase:**

• Bring focus to the community by helping to fund excellent science (including young investigators where needed), convening the community for sharing of ideas, and developing research collaborations across disciplines, institutions, countries, and sectors
• Employ the patients’ voice to help inform investigators about unmet medical needs
• Fund basic science and provide translational tools such as biosamples
• Develop natural history databases that are critical to characterizing the disease, identifying mechanisms of damage or potential therapeutic action, or exploring biomarkers

• Collaborate with NIH

• Educate and motivate the patient community to participate in, and advocate for, research

During the preclinical phase:

• Help fund preclinical studies needed to define the highest impact approaches for drug development and create a foundation for later-stage studies

• Engage in a knowledge-exchange with key academic or industry partners regarding the most promising areas of research, including helping to identify promising mechanisms of action and drug development targets

• Facilitate matchmaking between academic and industry partners

• Fund development of additional translational tools such as assays, cell and animal models, and biosamples

• Facilitate sponsor interviews with patients, key opinion leaders and PG leadership regarding natural history data, trial design and procedures, biomarkers and clinical endpoints, selection of subjects and sites, power calculations, consent forms

• Collaborate with FDA regarding FDA guidance, preclinical requirements, benefit-risk evaluation, education of FDA reviewers on the disease, and participation along with the sponsor in pre-IND meetings

During phase I:

• Provide clinical infrastructure including a network of sites, clinicians, and staff familiar with the patients and disease

• Provide information on unmet need and disease burden (may come from PG disease registry)

• Recruit participants promptly and effectively through a PG-developed patient registry

• Continue to educate and motivate patients and patient families

• Support patient costs for the trial

During phases II and III:

• Continue support provided in phase I

• Assist the research sponsor in determining the best trial design, including any consideration of barriers to entry or adapting the trial

• Conduct or participate in patient preference studies or benefit-risk assessments

• Provide recommendations and/or input into patient-reported outcomes (PRO) and quality-of-life instruments to be used in the trial

• Review patient-related trial materials (informed consent forms, educational materials)

• Assist with trial recruitment and/or serve as a peer advocate

• Serve on the DSMB for the trial

• Evaluate and advise on relevancy of collected data as they pertain to patients
• Assist in the development of patient-level communication at trial conclusion

**During FDA review and approval:**
• Accompany the sponsor to any post-phase II/III FDA meetings
• Provide a patient representative to serve on the FDA advisory committee
• Provide testimony for FDA hearings and advisory committee meetings
• Prepare submission for newborn screening when appropriate†

**During post-approval:**
• Work with the sponsor and payers regarding reimbursement
• Advise sponsor of gaps left by earlier clinical trials that can be addressed with additional postmarketing studies
• Assist in postmarket surveillance
• Provide communications support and feedback from the patient community via website, newsletters, blogs, email, and social media

4. **Select sponsors who have a product or program with significant promise for your constituents and who are committed to engaging in a meaningful way.**

Often this commitment becomes evident within the industry setting when the company’s pipeline has matured to the point of clinical testing, but PGs can also be proactive in soliciting industry focus in a particular disease space even earlier in the process based on their knowledge of emerging science. 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. The PG should be willing to collaborate with multiple partners and avoid exclusivity agreements. After appropriate potential partners have been identified, the PG should identify the right points of contact and key decision makers within the company or academic setting for their specific disease area.

Increasingly sophisticated PGs are developing advisory boards and other leadership processes that include members with diverse perspectives, experience, and backgrounds to assist the PG in laying out a strategy and action plan for meaningful engagement in the drug development process.

Make sure the PG’s senior leadership:
• Consists of diverse individuals well versed in the science of the disease area
• Understands the intricacies of therapy development and conduct of clinical trials

† For example, when the disease is not currently being screened for in newborns but the PG believes it can be shown 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.
5. **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. PGs should recognize that they should not be used by sponsors as marketing tools or to undermine the sponsor’s competitors. At the same time, it is inappropriate for PGs to expect preferential treatment or enrollment of subjects they refer for clinical trials—PGs should acknowledge and accept that all trial participants must meet standard eligibility requirements.

To manage internal and external conflicts of interest (COI) effectively, PGs should fully disclose relationships with industry sponsors in their internal deliberations and external transactions and be transparent and accountable in their publications, communications, and reporting (e.g., websites, newsletters, reports to the IRS) so as to build and maintain the trust of all stakeholders. However, PGs will not always be able to avoid real or perceived COI and so must learn to manage it effectively by abiding by the closely related principles of disclosure, transparency, and accountability. PGs should consult guidelines published by informal monitors such as Charity Navigator, Guidestar, and the Better Business Bureau to determine how best to manage internal COI. Other rules and regulations published by the Department of Treasury and FDA and findings of U.S. Congressional Committees can help in managing external COI.

- To help PGs navigate the complex web of decisions and opportunities, it is recommended that they prospectively develop a “Guiding Principles” document. This document defines how and with whom you will collaborate around research and development programs. It will serve to assure research sponsors that your organization will be respectful about issues like privacy and transparency in partnering with other sponsors, including competitors. The document will also serve to notify the sponsor of your expectations around issues like access to patient information, sharing of progress/results, and firm lines around what the PG will or will not do to support the trial. The following topics could be covered in this document:
  - Confidentiality
  - Working with competitors
  - Data sharing
  - Expectations for communication
  - Working with regulators (i.e., will you advocate for specific treatments/approvals or will you advocate only for general principles?)
  - Compensation policy for consulting
  - Expectations for expanded or continued access to research treatments
  - Ethical treatment of research subjects
Part IV. Figure

PG Engagement Across the Research & Development Continuum

- Input regarding interest of research question to patient community
- Providing data on unmet need & therapeutic burden
- Fundraising and direct funding for research to identify target molecules
- Facilitating collaboration with NIH
- Characterizing the disease & relevant mechanisms of action

- Fundraising & direct funding for research, trial operations support
- Assistance in selecting & recruiting optimum clinical sites
- Clinical infrastructure support
- Helping educate/motivate patient community & recruit for trials
- Providing patient feedback on participant experience
- Serving on Data & Safety Monitoring Board
- Input for any trial adaptations or modifications
- Performing or participating in benefit-risk and patient preference studies

- Serving on postmarket surveillance initiatives
- Helping return study results to participants
- Co-presenting results
- Publications/communications results
- Feedback on how patient community views results
- Natural history database & registry support
- Working with payers on reimbursement

Prediscovery | Preclinical | Phase I/II/III | FDA Review & Approval | PAS/Outcomes

- Fundraising and direct funding for research
- Providing translational tools (assays, cell & animal models, biosamples, biomarkers, etc.)
- Helping define study’s eligibility criteria
- Natural history database & patient registry support
- Input on meaningful clinical endpoints/PROs
- Assistance on informed consent form/process
- Working with FDA on benefit-risk and draft guidance
- Accompanying sponsor to pre-IND FDA mg to advocate for study

- Providing public testimony at the FDA Advisory Committee & other FDA hearings
- Preparing submission for newborn screening when appropriate

*Adapted from Parkinson’s Disease Foundation materials for CTTI’s Patient Groups & Clinical Trials Project

Abbreviation: PAS=post-approval studies
## Part V. Tools

### Tool 1. PG Organizational Expertise and Assets Evaluation Tool

<table>
<thead>
<tr>
<th>Activity</th>
<th>Pre-Discovery</th>
<th>Pre-Clinical</th>
<th>Phase 1/2/3</th>
<th>FDA Review &amp; Approval</th>
<th>PAS/Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input re interest of research question to patient community</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Providing data on unmet need &amp; therapeutic burden</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fundraising and direct funding for research to identify target molecules</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facilitating collaboration with NIH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Characterizing the disease &amp; relevant mechanisms of action</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helping define study's eligibility criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Providing translational tools (assays, cell &amp; animal models, bio-samples, biomarkers, etc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural history database &amp; patient registry support</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Input on meaningful clinical endpoints/PRO's</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assistance re informed consent form</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working with FDA re benefit-risk and draft guidance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accompanying sponsor to Pre-IND FDA mtg to advocate for study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fundraising and direct funding for research, trial operations support</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assistance in selecting &amp; recruiting optimum clinical sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical infrastructure support</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helping educate/motivate patient community &amp; recruit for trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Providing patient feedback on participant experience</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serving on Data &amp; Safety Monitoring Board</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Input for any trial adaptations or modifications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accompanying sponsor to milestone meetings, e.g., after phase 2 &amp;3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Providing public testimony at the FDA Advisory Committee &amp; other FDA hearings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preparing submission for newborn screening when appropriate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serving on post-market surveillance initiatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helping return study results to participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-presenting results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Publications/communications re results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feedback on how patient community views results</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working with payers re reimbursement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The highlighted cells indicate the phase(s) of the clinical trial continuum where the activity is most likely to occur.*
## Tool 2. Assessment of PG Internal Aspects: Focus

<table>
<thead>
<tr>
<th>Assessment of PG Internal Aspects</th>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vision/Areas of Focus: Are the PG's vision, mission, goals, and areas of focus clearly stated and reasonable?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do these statements seem to reflect sound judgment regarding the disease space and state of the science?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is commitment to these statements demonstrated in the PG's activities and performance?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do these statements seem reasonable relative to the PG's current or projected budget?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Operations: Are the PG's operational programs well structured, performing well, and demonstrating measurable impact?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If the PG awards grants, are awards made via a credible application and peer review process and do the awards reflect the vision, mission, goals and area of focus?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG have and make good use of solid scientific/medical professional staff and/or advisors?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG have an effective fundraising and budgeting process adequate to its vision, mission, goals and areas of focus?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG receive good ratings from charity monitors such as the Better Business Bureau and Charity Navigator?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG's collaborative model include partnering options for sponsors outside of grant-based options?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Budget and Fundraising: Do the PG's budget and fundraising programs seem adequate to its needs or show signs of being able to become so?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the PG been able to marshal the resources required to establish important assets for development (e.g., patient registry, natural history database, clinical network)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG devote a healthy percentage of its budget to its operational program vs. its overhead (e.g., administrative and fundraising costs)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG's budgets over the last 5 years demonstrate a fundraising capacity that is steady or growing and diverse in sources?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of PG Internal Aspects</td>
<td>YES</td>
<td>NO</td>
<td>N/A</td>
<td>Notes</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-----</td>
<td>----</td>
<td>-----</td>
<td>-------</td>
</tr>
<tr>
<td><strong>Communications: Does the PG have the communications systems needed to facilitate development across the full continuum?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG have sufficient internet and social media presence?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG issue a variety of publications to various audiences?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG use these communications effectively to educate, motivate and engage its patient community, medical, scientific, industry and government partners?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG use these communications effectively across all the phases of clinical development in which it is engaged?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Tool 3. Assessment of PG External Relationships: Other PGs

<table>
<thead>
<tr>
<th>Assessment of PG External Relationships</th>
<th>YES</th>
<th>NO</th>
<th>N/A</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relationships with Other PGs: Does the PG engage collaboratively with other PGs of interest?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG collaborate with other PGs in advocating for policy and budget initiatives beneficial for their public and private partners (patients, NIH, FDA, academia, industry)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG collaborate with other PGs in cofunding research of mutual interest?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG collaborate with other PGs in organizing or participating in meetings/conferences focused on best practices, lessons learned and insights gained in areas of mutual interest?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relationships with Academia: Does the PG engage collaboratively with academic and other research institutions, centers of excellence, etc.?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG collaborate with such institutions in funding research projects supportive of the PG mission?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG collaborate with such institutions in keeping academic investigators informed of funding opportunities of government agencies and other PGs?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG collaborate with such institutions in supporting academic investigators’ grant applications to these other funding sources?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG collaborate with such institutions in encouraging and facilitating scientific collaborations?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relationships with Industry: Does the PG engage collaboratively with industry partners?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG facilitate discussions between industry and academic &quot;discovery&quot; scientists?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG have and make available assets needed to assist industry partners throughout the development cycle (e.g., registry, natural history, translational tools, key opinion leaders)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG help de-risk early-stage development by funding or cofunding discovery, translational and clinical work?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG educate, motivate and recruit patients so that clinical trial enrollment, compliance and retention are optimal?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of PG External Relationships</td>
<td>YES</td>
<td>NO</td>
<td>N/A</td>
<td>Notes</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----</td>
<td>----</td>
<td>-----</td>
<td>-------</td>
</tr>
<tr>
<td><strong>Relationships with Patients:</strong> Does the PG's relationship with patients and their families enable the PG to:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Communicate effectively with the patient population?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obtain robust registration in a patient registry?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motivate patients to participate in a natural history study?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obtain sufficient patient biosamples to assist in preclinical studies?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educate, motivate, and engage patients so that clinical trial enrollment, compliance and retention are optimal?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assist in post market surveillance?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relationships with the NIH:</strong> Does the PG engage collaboratively with NIH institutes and centers (e.g., disease-specific institute and NCATS)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG maintain dialogue with program officer and appropriate offices of special interest (e.g., translational or clinical staff, Office of Rare Disease Research, TRND, BrIDGs)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG maintain two-way communication between NIH and the PG's other stakeholders (e.g., keeping NIH staff informed of the status of research and needs of the disease community, keeping the PG's academic and industry partners aware of NIH opportunities, submitting letters of support for NIH applications, participating as co-applicant for NIH programs when appropriate)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG participate in the functions of the National Advisory Councils of the NIH institutes and centers of interest?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relationships with the FDA:</strong> Does the PG engage collaboratively with the appropriate centers and offices of the FDA (e.g., CDER, CBER, and CDHR review divisions, Office of Orphan Product Development, Rare Disease Program)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG help educate these FDA personnel regarding the disease, its unmet medical needs, benefit risk evaluations, etc. (e.g., include FDA personnel in the PG's scientific conferences, brief FDA personnel at FDA workshops and symposia)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG work with its academic and industry partners in preparing IND submissions, participating in pre-IND and other milestone meetings?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of PG External Relationships</td>
<td>YES</td>
<td>NO</td>
<td>N/A</td>
<td>Notes</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----</td>
<td>----</td>
<td>-----</td>
<td>-------</td>
</tr>
<tr>
<td>Does the PG have patient representatives designated as FDA special government employees ready to serve on FDA Advisory Committees and as members of the FDA teams at milestone meetings with industry sponsors?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relationships with Congress: Does the PG engage congressional representatives regarding issues of key interest to its patient community?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG encourage its community members to engage their elected representatives in support of legislation beneficial to them (e.g., more robust budgets for the NIH and FDA, policy provisions intended to benefit and improve NIH and FDA operations, newborn screening)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does the PG collaborate with other PGs in organizations aimed at concerted efforts to work with Congress in support of beneficial NIH and FDA budgets and policies (e.g., Research America, Alliance for a Stronger FDA)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BrIDGS=Bridging Interventional Development Gaps; CBER=Center for Biologics Evaluation and Research; CDER=Center for Drug Evaluation and Research; CDRH=Center for Devices and Radiological Health; FDA=Food and Drug Administration; IND=investigational new drug; NCATS=National Center for Advancing Translational Sciences; NIH=National Institutes of Health; TRND=Therapeutics for Rare and Neglected Diseases
Part VI. Glossary

For the purposes of this publication, the following definitions are provided.

**Academic investigator.** An individual engaged in the conduct of scientific research at an academic institution.

**Clinical trial enterprise.** A broad term that encompasses the full spectrum of clinical trials and their applications. It includes the processes, institutions, and individuals that eventually apply clinical trial findings to patient care.

**Conflict of interest (COI).** A set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest. Internal COI is a conflict of interest that pertains to individuals within an organization (e.g., directors, officers, staff and advisors of a PG). External COI is a conflict of interest that pertains to the organization itself in its dealings with other organizations (e.g., in a PG's dealings with its industry or academic partners).

**Master services agreement.** An overarching contract that details the responsibilities and obligations of the parties to each other. This comprehensive contract generally includes detailed rates, services, and terms for each functional area of the partnership with addenda or statements of work for specific activities to be conducted.

**Memorandum of Understanding (MOU).** Often the first stage in the formation of a formal contract. An MOU is more formal than a handshake and is given weight in a court of law should one party fail to meet the obligations of the memorandum.

**Non-Disclosure Agreement (NDA).** A legal contract between at least two parties that outlines confidential material, knowledge, or information that the parties wish to share with one another for certain purposes, but wish to restrict access to or by third parties. An NDA is also known as a confidentiality agreement, confidential disclosure agreement, proprietary information agreement, or secrecy agreement.

**Patient-Focused Drug Development (PFDD).** An FDA initiative seeking a more systematic approach to obtaining patients’ input on specific disease areas, including their perspectives on their condition, its impact on daily life, and available therapies.

**Patient Groups (PGs).** A term encompassing patient advocacy organizations, disease advocacy organizations, voluntary health agencies, nonprofit research foundations, and public health organizations. For clarity of focus, our use of the term PGs is not meant to refer to individual patients or advocates.

**Patient preference or benefit-risk assessment.** A study of patient preferences related to therapies and outcomes regarding willingness to accept uncertainty and trade-offs based on potential harms versus benefits. Benefit-risk assessments may also seek to identify subgroups of patients in a heterogeneous population based on preferences.

**Patient-Reported Outcome.** Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.
**Payer.** In health care, generally refers to entities other than the patient that finance or reimburse the cost of health services. In most cases, this term refers to insurance carriers, other third-party payers, or health plan sponsors (employers or unions).\(^5\)

**Phases of clinical trials.** Different steps in a trial, each with its own purpose and designed to help researchers answer different questions. Phase I involves an experimental drug or treatment in a small group of people (e.g., 20–80) for the first time to evaluate its safety and identify side effects. In phase II, the experimental drug or treatment is administered to a larger group of people (e.g., 100–300) to determine its effectiveness and to further evaluate its safety. In phase III, the experimental drug or treatment is administered to large groups of people (e.g., 1,000–3,000) to confirm its effectiveness, monitor side effects, and compare it with standard or equivalent treatments. In phase IV, after a drug is licensed and approved by the FDA, researchers track its safety, seeking more information about its risks, benefits, and optimal use.

**Quality of life.** A multidimensional concept that includes domains related to physical, mental, emotional, and social functioning.

**Research and Development (R&D).** A planned series of future events, items, or performances of research and medical product development activities.

**Research sponsors.** An individual, institution, company, or organization (for example, a contract research organization) that takes the responsibility to initiate, manage, or finance the clinical trial.

**Stakeholders.** Parties with concerns or interests in an organization, endeavor, or initiative.

**Standard work practice.** A written description of how a process should be done in order to ensure consistent execution.
Part VII. References


5. Mosby’s Dental Dictionary, 2nd edition. © 2008 Elsevier, Inc. All rights reserved.

These recommendations are based on results from the Patient Groups & Clinical Trials project.
CTTI’s Executive Committee approved the recommendations.
Released in October 2015