CTTI Recommendations: Patient Groups & Clinical Trials

October 2015

CTTI MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

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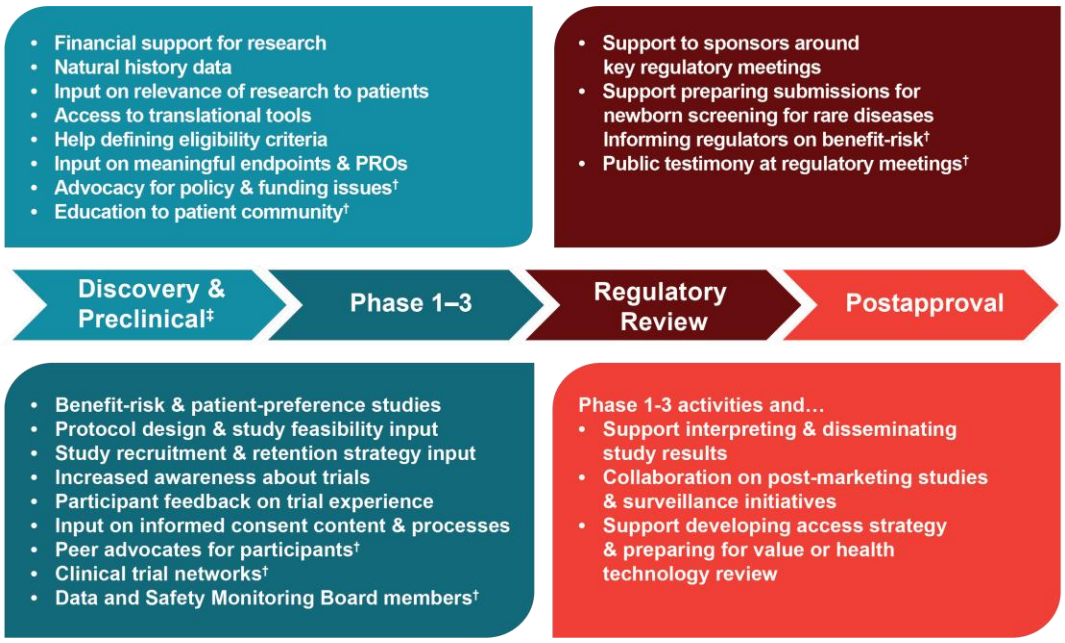
OVERVIEW: Realizing the Value of Effective Patient Group Engagement

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.[1] 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.

However, 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" to encompass 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 patient groups is not meant to refer to individual patients or advocates,

although patient groups 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 patient groups throughout the research and development continuum. These collaborations will enhance the voice of the patient in all aspects of the clinical development process.

These evidence-based recommendations were developed by experts and leaders across the clinical trials enterprise, including patients, industry sponsors, academic investigators, and other stakeholders. These recommendations will be valuable for all stakeholders and ultimately will help the research enterprise maximize the opportunities of patient engagement around clinical trials.

CONTENTS AT-A-GLANCE

I. 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' voices) in the early stages of disease targeting, making full use of patient group input while clinical trials are still in the planning phase to help shape and refine the study protocol (see Patient Group Engagement Across the Clinical Trial Continuum and Patient Group Organizational Expertise and Assets Evaluation Tool). Soliciting patient group 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.

Patient groups and research sponsors often have different backgrounds and perceptions of the value that patient representatives bring to the trial, or the tasks that patient groups 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 patient group 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 patient groups 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 patient group if they have funded the study or have invited the sponsor to participate in their development program. Expectations about the role of patient group 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 patient groups. Confidentiality Agreements (CAs) and Non-Disclosure Agreements (NDAs) allow sharing of sensitive information with patient groups for this purpose. Patient groups must abide by CAs and NDAs they sign with sponsors to enable open communication. Similarly, patient groups have confidential information they may wish to protect and sponsors should abide by NDAs signed with patient groups.

4. Involve the expertise of multiple partners for a broader perspective to mitigate risk and enrich pipeline development.

Patient groups 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 patient group 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 patient groups. In fact, as demonstrated by Janet Woodcock's statements at the Expert Meeting,[2] 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 patient group engagement. It is important to clarify which kinds of interactions with patient groups 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 patient groups in planning and conducting clinical trials. Patient groups 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 patient group 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 patient groups should convey the information about the trial as approved by the Institutional Review Board (IRB).

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

- Patient groups 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 patient group to do certain work with a tangible end-product, the patient group should be compensated fair market value.
- Patient groups 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 patient group must have independence.
- Patient groups as non-compensated collaborators.

To avoid actual or perceived improper influence by patient groups, research sponsors should proactively establish their own rules of engagement. In any type of patient group engagement, an NDA may be appropriate depending on the level of disclosure of commercial, confidential, or trade-secret information to the patient group. It is important for research sponsors to understand their institution's legal, regulatory, and research administration requirements before engaging with patient groups. Before selecting a type of patient group 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 patient group engagement, should review plans, to ensure that appropriate, but not overly conservative, measures are taken. Patient groups 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.

Case Example

In the three years that Bristol-Myers Squibb's Clinical Trials Diversity and Patient Engagement and Legal teams have been working with patient groups, they have outlined the following general types of patient group engagement depending on the interaction

1. Service provider engagement: patient group acts as a service provider, consultant or vendor on a contractual basis. Patient group agrees to do certain work with a tangible end product and is compensated at fair market value.
2. Corporate/charitable giving: The company provides a grant to support patient or other relevant education projects done by a patient group that has 501(c)(3) tax-exempt status. To mitigate risk, the patient group project content and activities are developed independent from the sponsor.
3. Non-compensated collaboration interactions: Interactions with patient groups that might require a confidentiality agreement and do not involve compensation. These collaborations are mutually beneficial to industry and the patient group's population being served.

Recognizing that not all interactions are created equal, each interaction is pressure-tested against the above three areas to inform subsequent steps for engagement. It should be noted that each area has its own contractual rules and parameters to mitigate risk.

II. Recommendations for Research Sponsors—Industry and Academia

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

For industry research sponsors, the primary drivers for patient group 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 patient group 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 patient group engagement on clinical drug development. Awareness will help minimize resistance, provide examples of successful patient group 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 patient group engagement.

Research sponsors need to develop and execute a comprehensive roadmap for substantive patient group engagement. These plans should encompass early Research and Development (R&D) through later stage clinical development. Fragmented relationships and unstructured patient group 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 patient groups, especially when multiple divisions are reaching out to patient groups. 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 patient group collaborations that can advance clinical development activities and clinical trials (see 4 below).

Last, it will be critical to achieve appropriate resourcing to support patient group engagement. Specific and dedicated funding for patient group activities should be prospectively built into clinical development programs, study budgets, and corporate support mechanisms to ensure timely, productive, and continuous engagement with the patient group.

2. Match patient group 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 patient groups. Ideally, sponsors should select patient groups 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 patient group. This gap was identified in the interview process and Expert Meeting. CTTI has developed an infographic and accompanying tool on patient group engagement across the research and development continuum that can be used to analyze patient group skills and strengths, assigning those to different phases of drug development having the greatest relevance. To demonstrate how sponsors can help, patient groups 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 patient group expertise, interests, organizational capacity, and relationships (see Patient Group Organizational Expertise and Assets Evaluation Tool, Assessment of Patient Group Internal Aspects: Focus Tool, and Patient Group Organizational Expertise and Assets Evaluation Tool). When engaging with a patient group, the sponsor needs to know about the patient group'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 patient group before engagement.

Further, research sponsors should match assigned tasks to the group's strengths. For example, a patient group 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 patient group 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 patient groups without driving the agenda. Sponsors can connect patient groups with experts who support their engagement in research activities.

3. Ensure that patient groups are essential partners throughout the R&D process and not token voices.

Research sponsors should recognize that the most successful partnerships with patient groups are those in which both entities are full partners at the outset, working toward the same goals from different perspectives. CTTI's Prioritization Tool for Sponsors and Patient Groups can help identify opportunities for collaboration with high value for all stakeholders. Engagement with patient groups should involve a discrete division of labor in which each group contributes its unique area of expertise.

Partnerships with patient groups must not be limited to phase 3 of the trial. The learning acquired through preclinical engagement and during phases 1 and 2 should be incorporated into the phase 3 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 patient groups 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 patient groups 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 patient groups 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 and 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 patient groups.

Sponsors should establish and document best practices for engaging with patient groups, 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 patient group 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 patient groups
- Identify parties responsible for relations with patient groups if there are multiple people making contact with them
- Drive transparent communication between the research sponsor and patient group
- Define and implement contracting and communication plans

5. Measure the impact of patient group engagement.

Though no standard metrics exist for patient group 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 patient groups 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 1 and 2 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 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 patient groups and communicate openly with them on a regular basis.

In addition to involving patient groups early, study teams should communicate with them regularly throughout in the development program. Research sponsors should let patient groups 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 patient groups 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.

III. 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 patient group 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 patient groups 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 patient groups or umbrella patient groups 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.

Patient groups 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. Patient groups 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[3]
- 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, patient groups 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.

Patient groups 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 (see Patient Group Engagement Across the Clinical Continuum and Patient Group Organizational Expertise and Assets Evaluation Tool). Active engagement involves sharing the patient group'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 patient groups
- 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 patient group 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 patient group as a key player in the field.

Patient group engagement could involve the following activities.

During the discovery 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 patient group 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 1:

- 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 patient group disease registry)
- Recruit participants promptly and effectively through a patient group-developed patient registry
- Continue to educate and motivate patients and patient families
- Support patient costs for the trial

During phases 2 and 3:

- Continue support provided in phase 1
- 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 regulatory review:

- Accompany the sponsor to any post-phase 2/3 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[a]

[a] For example, when the disease is not currently being screened for in newborns but the patient group 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.

During postapproval:

- 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 patient groups 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. Patient groups 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 patient group should consider establishing a scientific review process in order to have an independent ability to evaluate the science being presented. The patient group should be willing to collaborate with multiple partners and avoid exclusivity agreements. After appropriate potential partners have been identified, the patient group should identify the right points of contact and key decision makers within the company or academic setting for their specific disease area. CTTI's Prioritization Tool for Sponsors and Patient Groups can help identify opportunities for collaboration with high value for all stakeholders.

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

Make sure the patient group'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
- Understands key business and policy issues in order to provide sound advice on which academic and industry partners to engage and in what manner

5. Manage real or perceived conflicts of interest by establishing policies that require full disclosure, transparency, and accountability.

Patient groups 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. Patient groups 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 patient groups to expect preferential treatment or enrollment of subjects they refer for clinical trials—patient groups should acknowledge and accept that all trial participants must meet standard eligibility requirements.

To manage internal and external conflicts of interest (COI) effectively, patient groups 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, patient groups 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. Patient groups 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 patient groups 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 patient group 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

IV. Glossary

The following definitions are provided for the purposes of this publication.

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 patient group). External COI is a conflict of interest that pertains to the organization itself in its dealings with other organizations (e.g., in a patient group'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. 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 patient groups 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 (PRO). 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).[4]

Phases of clinical trials. Different steps in a trial, each with its own purpose and designed to help researchers answer different questions. Phase 1 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 2, 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 3, 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 4, 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.

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ABOUT THE RECOMMENDATIONS

- These recommendations are based on results from CTTI's Patient Groups and Clinical Trials project.
- CTTI's Executive Committee approved in October 2015.
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- All of CTTI's official recommendations are publicly available. Use of the recommendations is encouraged with appropriate citation.

ABOUT CTTI

Clinical Trials Transformation Initiative (CTTI), a public-private partnership co-founded by Duke University and the U.S. Food and Drug Administration, seeks to develop and drive adoption of practices that will increase the quality and efficiency of clinical trials. Comprised of more than 80 member organizations—representing academia, clinical investigators, government and regulatory agencies, industry, institutional review boards, patient advocacy groups, and other groups—CTTI is transforming the clinical trials landscape by developing evidence-based solutions to clinical research challenges. Many regulatory agencies and organizations have applied CTTI's nearly 20 existing recommendations, and associated resources, to make better clinical trials a reality. Learn more about CTTI projects, recommendations, and resources at www.ctti-clinicaltrials.org.