A BioPontis Alliance Report

Integrating Rare Disease Patients into Pre-Clinical Therapy Development;
Finding our Way with Patient Input

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ABSTRACT

Patient integration into drug development is being emphasized by many regulatory authorities, patient organizations, coalitions and pharmaceutical companies. However, that effort rarely if ever extends into the earliest drug discovery and preclinical phase, when the actual therapeutic strategy is set. The over 7,000 rare diseases represent a huge diversity of illnesses with frequently poorly understood clinical presentation and progression. Therapeutics development in this arena must be addressed far more efficiently, which means that patient input needs to enter strategy development at the very beginning of drug discovery. In addition, patient involvement should improve the later experience in clinical trials, regulatory review and commercial delivery of treatment to patients.

The current effort was designed to define methods and practices that enable the integration of patients into the drug discovery and pre-clinical stages of development. We saw a clear need to engage first in a direct dialogue with patient organization leaders to learn about what is important to patients and to co-develop practical methods for this new way of working between scientists, clinicians and patients. The results of two workshops, held with patients’ organizations within the rare neurological disease community, are described. The objective of these initial workshops was to initiate a new patient integrated procedure starting in the earliest stages of therapeutics development, to be transferred to product development companies for the transition to clinical development, regulatory approval, and distribution to patients.

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Integrating Rare Disease Patients into Pre-Clinical Therapy Development; Finding our Way with Patient Input

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A significant shift is underway in how regulators, pharmaceutical companies and researchers are viewing the role of patients in the design and implementation of therapy (medicines) development. As noted by the European Patients Academy on Therapeutic Intervention¹:

“There is an industry-wide move towards patient focus, with the creation of Patient-Centered Outcomes Research Institute (PCORI)², FDA’s Patient-Focused Drug Development (PFDD) initiative³, Clinical Trials Transformation Initiative (CTTI)⁴ and the Patient Focused Medicine Development (PFMD) coalition⁵ and others. ... Experience to date demonstrates that close cooperation with patients has resulted in increased transparency, trust and mutual respect between them and other stakeholders. It is acknowledged that their contribution to the discovery, development and evaluation of medicines enriches the quality of the evidence and opinion available.⁶

EMA and FDA have highlighted specific objectives in their guidances and official position statements; such as beginning the collection of natural history data earlier, ‘listening carefully to patients and organizations that represent them to learn more about how they perceive benefits, risks, and unmet needs’⁷ and to “more systematically obtain the patient’s perspective on a disease and its impact on patients’ daily lives, the types of treatment benefit that matter most to patients, and the adequacy of available therapies for the disease

Development of therapies for rare diseases is increasingly becoming a testing ground for best practices in patient engagement as well as use of surrogate markers, biomarkers and flexible design of human trials. This is all driven by the special challenges of working in narrowly defined (e.g., by specific genetic mutation) patient populations⁸. Indeed, rare disease patient organizations have themselves led the

² http://www.pcori.org/about-us
³ http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm
⁴ http://www.ctti-clinicaltrials.org/
⁵ http://patientfocusedmedicine.org/
initiation and advancement of several recently approved disease modifying, genotype specific therapies (Cystic Fibrosis Foundation, Parent Project Muscular Dystrophy). Even so, the primary entry point for patient or care-giver perspectives has continued to remain at the time of recruitment for first clinical trials. This is due in part to a frequently arms-length relationship between commercial drug developers and patients in the drug discovery and preclinical development stage, which is seen by commercial developers as a purely technical phase. The inclusion of non-experts in the science and clinical aspects of drug development has simply not been considered relevant to success especially during the early, more purely technical stages.

In the rare disease field, patient populations are more knowledgeable about their diseases compared to most clinicians and scientists because few professionals have exposure to enough patient’s lifetimes to accumulate deep disease knowledge or experience. Additionally, the lack of a patient-derived natural history data set before initiation of a product development cycle can greatly increase the risk of failure in rare disease therapeutics development.

The nonprofit BioPontis Alliance for Rare Diseases is focused exclusively on the earliest stages of therapy development for rare neurological diseases. Given the background presented above, we have reasoned that if patients can be meaningfully integrated into the earliest stages of drug discovery, e.g., defining therapeutic objectives, identifying relevant symptom measurements and disease progression markers or the development of relevant outcome measures, this could greatly improve the likelihood of achieving the treatments that patients truly need and want. In addition, this involvement could improve the later experience in clinical trials, regulatory review and access to treatment for patients. We therefore have committed to discovering practical methods, practices and tools for incorporating patients directly into our pre-clinical development programs. Our proposal to integrate patients is novel at this early pre-clinical translational stage of treatment development, and we seek to establish practices that can be widely utilized across all rare diseases – not just for one product or rare disease.

Because we propose to break new ground, we were faced with a clear need to engage first in a direct dialogue with patient organization leaders to learn about what is important to patients and to co-develop practical methods for this new way of working between scientists, clinicians and patients. To achieve these objectives, patient organization workshops were conducted in 2016 in the US and Europe.

This white paper describes the results of the first two workshops, held with patients’ organizations within the rare neurological disease community. Two critical factors that can change the direction and emphasis of the development program were explored: the creation of a vision for the new therapy ("target profile") at the beginning of the therapeutics discovery effort guided directly by patients integrated formally into the therapy development team, including participation in assessment of likely risk/benefit and proposed endpoint relevance to disease outcomes at the point where a lead candidate therapy has emerged and must be optimized for clinical trials.

**Methods and design of Patient Integration Workshops (PIWs)**

Eight (US) and nine (EU) representatives of rare neurological patient organizations were invited to participate in each of two single-day-long Patient Integration Workshops, one held in Washington D.C. on April 19 and one in Leuven, Belgium on June 14, 2016.
Our thanks go to the following participating organizations.

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<thead>
<tr>
<th>Europe</th>
<th>United States</th>
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<tr>
<td>Alternating Hemiplegia Federation of Europe</td>
<td>Association for Frontotemporal Degeneration</td>
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<td>CMT-France</td>
<td>Batten Disease Support and Research Association</td>
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<td>Dravet Syndrome Foundation</td>
<td>Ehlers-Danlos Syndrome Society C.A.R.E.S.</td>
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<td>European Huntington Society</td>
<td>FSH Muscular Dystrophy Society</td>
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<td>Friedrich Ataxie Förderverein e.V.</td>
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<td>Liga Myasthenia Gravis</td>
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<td>NBIA, Telethon Italia and Rare Epilepsy</td>
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Before each PIW, participants were sent background information on the drug discovery and development process. At each meeting, the key aspects of this process were reviewed (see Figure 1 for an overview of the development process). Three phases of the drug discovery process were identified as being important points for patient input and participation; 1) The initiation step when the characteristics of the desired therapy are defined as objectives for the drug discovery process; 2) the refinement stage when animal toxicity and optimization of the drug molecule for absorption, delivery to the affected organs, metabolism, etc are achieved; and 3) the final stage when preparation for and definition of the proposed human trials is being developed.

![The drug discovery process](image)

**Figure 1.** Overview of the drug discovery and preclinical drug development process as exemplified by small molecule drug therapeutics.
The group was also introduced to an overview of the different types of therapeutic molecules or technologies that could be chosen to develop for any given rare disease (Figure 2). The rationale for which technology to choose for a specific disease target was discussed with the important outcome that patient representatives had new appreciation for the merits and challenges of well-established drug types (e.g., ‘small molecules’ or antibodies) versus newer technologies such as gene therapy. Since many rare diseases are caused by genetic defects, gene therapy was seen by many participants to be the most direct and effective therapy. As such, this discussion revealed how important it would be for patient organizations to consider the merits of pursuing only this higher risk, more complex therapy vs balancing with other well-established and less complex chemical compounds (small molecules) or protein (biologics) therapies.

<table>
<thead>
<tr>
<th>Advantages/Disadvantages of Developing Different Types of Therapeutics</th>
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<tr>
<td><strong>Small Molecule Drugs (SMDs)</strong></td>
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<tr>
<td><strong>Definition.</strong></td>
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<td><strong>Pro</strong></td>
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<tr>
<td>1. High-throughput screening for rapid discovery of hits 1. Often take advantage of established example of “normal” pathways 1. Can most directly treat the actual cause of the disease 1. Can keep mutant protein from being expressed</td>
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<td>2. Precise control of drug structure and purity         2. Frequently lower risk for toxicity than SMDs 2. Can provide a long-term “cure” or remission 2. Can be dosed chronically</td>
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<td>3. Highly tunable structures to optimize pharmacokinetics and effects on target 4. Relatively cheap to manufacture and can often be given orally 3. Can interact with nearly all biological targets, unlike SMDs 3. Can interact with nearly all biological targets, unlike SMDs</td>
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<td><strong>Con</strong></td>
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<td>1. Toxicity can be hard to predict 2. Small molecule therapeutics are not always possible to achieve for the disease target 1. Toxicity can be hard to predict 2. Expensive to produce 3. Usually i.v. administered 4. Can lead to antigenicity, ranging from loss of activity to autoimmune reactions to extreme allergic reaction 1. Supersensitive insulin receptors 2. Supersensitivity to low-dose insulin</td>
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<tr>
<td>2. Expensive to produce 3. Cannot be completely structurally resolved to assure purity 3. Usually i.v. administered 4. Can lead to antigenicity, ranging from loss of activity to autoimmune reactions to extreme allergic reaction 4. Cancer risk (for non-homologous recombination)</td>
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**Figure 2.** Overview of types of therapeutics

Following this introduction, participants discussed several examples of the types of inputs they might be asked to give at various stages of the drug discovery and preclinical development process (Figure 3). The group also covered what types of activities patient organizations already undertake and could expand upon to inform the development process such as registries, tissue banks, basic research support into target biology, clinical endpoint definitions (including patient-reported outcomes) and how to achieve best practices within a patient/drug developer collaborative framework.
<table>
<thead>
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<th>Topic</th>
<th>Questions</th>
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| Defining product features    | ▪ What symptoms of the disease are most disturbing to daily life?  
▪ How do you prioritize the importance of the different disease symptoms?  
▪ How might you measure those most troublesome symptoms?  
▪ At what age does the disease cause the greatest changes? What kind of patients are most severely affected and/or might best be able to show a positive drug effect, if there is one?  
▪ Would you be satisfied to hold the disease progression in check or is an actual improvement in symptoms the only path forward? |
| Optimize lead candidates     | ▪ What levels of risk are you comfortable taking in trying novel treatments? What type of risks would you tolerate for what levels of efficacy?  
▪ What is the maximum dosing frequency you could reliably manage without affecting your activities of daily life? How do these maxima change as efficacy increases?  
▪ Which routes of administration could you consistently and reliably manage?  
▪ How do you rate different routes of administration against each other? |
| Preparation for clinical entry | ▪ Are you willing to share your thoughts on the target profile and the preclinical results you have seen with regulators (e.g., FDA, EMA)?  
▪ Are you willing to attend regulatory meetings alongside the sponsor?  
▪ Are you willing to participate in a patient registry and longitudinal studies that assess the progression of your disease?  
▪ Are you willing to participate in clinical trials testing new drugs? |

**Figure 3.** Examples of potential patient inputs.
A proposed patient-oriented drug development process

1. Target Product Profile

Patient representative and workshop participants agreed on the following sets of inputs that patients and drug development scientists should bring to the table at the beginning of a rare disease drug discovery program and what the output of that process should be (Figure 4).

Drug discovery and development begins with assembling the biologic knowledge about the disease, and the molecular pathways involved, to design a scientific plan of attack on the disease; the "therapeutic rationale". Should the aberrant gene be silenced, or should the aberrant protein from that gene be antagonized or altered to become effective in some way, or should the biochemical pathway that the aberrant protein participates in be altered at some other point, all to correct the disease presentation? Given the strategy, what technology should be used? Decisions will be made on whether small molecule drugs or protein biologics or RNA silencing constructs, gene therapy or cell therapy technologies offer the greatest chances for success. Based on the strategy and the type of drug sought, assays using normal and diseased tissues or animal models of the disease will be created to see if therapy candidates can correct the defect. Finally, the therapeutic strategy and knowledge about the disease process will be used to propose serum or tissue biomarkers as well as clinical endpoints that could be reflective of the disease process or stage and that hopefully could be sensitive to therapeutic effects.

In order to create a shared target product profile for the drug discovery and development effort, patient organizations and the drug development team would combine their ideas on all these points to come to agreement on the profile of the therapy they are seeking. For example, patients will provide information on what disease symptoms are most relevant to their daily lives and the drug development...
team will relate that information to the animal model features they propose to measure and the related clinical endpoints that could later be studied. They could determine whether halting disease progression is sufficient or whether short-term symptom improvement and gain of function is a minimum requirement. The parties could determine what sorts of side-effects might be expected from the chosen therapeutic strategy and which ones might be tolerable long term and which must be avoided so as not to worsen quality of life even more. They could also set down which methods for administering the therapy (oral, injection e.g.) are practical as opposed to impractical, given the proposed benefit level and the patients’ limitations to administer medications.

Patient organizations, because of their knowledge of their disease and their advocacy with their expert clinicians, scientists and philanthropic donors, are best suited to be the drivers behind the development and use of diagnostic (often genetic) tests that help define the patient population that could benefit from the drug under development. From there, they can assemble identified patients onto organized patient registries and work with clinical specialists in their disease to initiate longitudinal natural history studies. The functions of those studies are to fully describe the variety of clinical presentations of patients with the disease and to determine how that presentation progresses over time. In so doing, they will discover which types of assessments are most sensitive and reliable to disease progression and will use that knowledge as a basis for designing better assessments that could be used in clinical therapy trials (“clinical endpoints”). To advance biological knowledge of the basis of their disease, patient organizations can and do work with investigators to create tissue banks so that researchers have access to relevant samples to study how the disease affects specific genes, gene expression and biochemical pathways.

The need for well-developed patent protection was raised from the perspective of the future commercializing company. While patient organizations were/are aware of this, it was not clear to most how to ensure that this effort is safeguarded during the discovery stages of research in the academic institutions where their grantee researchers are working. Moreover, the patient organizations sought guidance on whether or how to secure rights to the patents that may be filed as a result of their sponsorship of research. Looking forward, the groups agreed that some specific guidance was needed for them on how to participate in making sure that new intellectual property (IP) is created, registered and managed, so that research materials are available to all researchers interested in working on the disease.

2. Lead optimization stage: assessment of risk-benefit profile and proposed clinical endpoint relevance.

At this point in the therapy development process, candidates have been found that are not only positive in the screening assays, but have also been confirmed to exert their effects in accordance with the proposed therapeutic rationale. In addition, they appear to have sufficient potency, bioavailability, selectivity and safety for further development, the eventual goal being an application for clinical trials (IND (US FDA) or CTA (European EMA)). Now that far more is known about the therapy properties, the target product profile, or vision of the therapy, can be updated. More targeted assessments can be made specifically on whether the therapy appears to be doing something useful and whether or not there is too high a safety or convenience price for that benefit (Figure 5).
Figure 5. Re-evaluation at the lead optimization stage of drug development of proposed therapy risk-benefit and patient-relevant clinical endpoints.

3. Preparation for Clinical Trials

During this final phase of preclinical development, the alignment of the scientific and clinical team to the integration of the patients should be particularly close. Some of this alignment was obvious to both scientists and patient representatives, others were revelatory. For example, the design of the earliest Phase I/II clinical trials, including the inclusion and exclusion criteria, was expected to benefit from patient awareness and input. By contrast, when patients learned how challenging it can be to design and implement a manufacturing process that can be scaled from research lab to human dosing studies there was immediate appreciation for why availability of product can limit and stall trials; understanding this could lead to patience and support for problems that might arise later.

Referring back to the earlier stages of the process when the expansion or initiation of registries would be conducted by patient organizations, the workshop participants could easily see how valuable this proactive approach would be at the final stage when the plan for initiating clinical trials is underway. Moreover, patients could readily see how their participation in the development team would provide them with a more in depth understanding of the therapy that will now be offered to patients in the proposed clinical trial. Patients reflected how much easier it would be to educate their communities on the particulars of the drug and the trial, having been part of the process for both.
**Specific Points of Consensus**

The following points emerged from the discussions during the workshops.

1. Joint work between patient organizations, investigators and pharmaceutical companies is necessary for the creation and use of tissue banks to support biomarker development. Tissue from these banks needs to be available to all researchers, which has frequently not been the case in the past.

2. There was consensus that **longitudinal studies** are crucial in gaining a clearer understanding of the range of clinical presentations in the patient population, assessing disease progression and in setting up better clinical endpoints for clinical trials of therapeutics. Such studies benefit greatly by collaboration between patient organizations, clinicians, biomarker researchers and potential drug developers.
   - Biomarkers and surrogate endpoints can strongly support or indeed drive pivotal trials but need to be identified in early development and supported by biobank resources more openly.
   - Patient narratives can add strongly to endpoint development but are problematic a) for inclusion in registries and b) with regard to continuous data submission over time (without being burdensome to patients).

3. Development of **target profiles** for drug discovery and **novel endpoints** could be key areas of interaction between drug developers and patient groups.

4. Patient organizations struggle to maintain focus of their efforts along an organized path to therapeutic development and to understand what the prerequisites are at each step. It would be valuable for patient organizations to have a **development readiness inventory tool**. This tool would allow patient organization boards to target funds more effectively and patient organizations to organize and execute their research meetings better. Immediately after the workshops, the authors worked with patient organization representatives to draft and pilot the tool.

5. Patient organizations would like to collaborate on a template for contracts covering **ownership and access to intellectual property (IP)**, animal models and cell lines so that access and IP security are assured. Patient organizations were supportive that the drug developers own the IP in joint projects in a model where the financial benefits can be shared with all participants as projects mature.

6. Drug developers need **patient input** to advance a new therapeutic to the IND stage, but patient willingness to share information varies by disease. Patient groups could show patients how important the data can be by sharing a case in which patient input drove success in development.

7. There is no formal mechanism in place for patient organizations to help their member patients assess **risk-benefit aspects** of new therapeutics before entering a clinical trial. There was support for the idea of developing a list of questions for patients to consider and educational materials on what to expect in a trial before participating in a trial.
   - That would not only potentially improve recruitment but also patient retention in ongoing studies.
b. In order to do this effectively, patient organizations need their partners (pharmaceutical companies) to disclose more information about the therapeutic, the development plan and potential risks.

c. Risk appetite of patients is highly dependent on the patient’s current quality of life and the predicted level of efficacy of the new therapeutic.

8. There was consensus that a number of lessons can be learned from recent examples of orphan drug approval discussions. They strongly support the contention that companies must work even more closely with patient organizations. Relying on the organization’s understanding of the disease, a drug developer is in a better position to define endpoints and inclusion criteria for clinical trials.

**Background of the Initiative: BioPontis Alliance for Rare Diseases**

BioPontis Alliance for Rare Diseases is dedicated to the 350 million children and adults living in shadow around the world, afflicted with devastating diseases too rare to be noticed. Genetic causes are known for many and technology to create treatments is available, yet only 5% have any treatment. Academic researchers find causes but cannot generate medicines. Pharmaceutical developers frequently cannot justify risky, early-stage investment for such small populations. Patient organizations want progress but lack expertise. BioPontis has designed a novel ‘Productivity Alliance’ model that unites these communities into an efficient system for parallel development of many therapies.

Importantly, ultimate success in bringing treatments to patients relies on the pharmaceutical industry doing their part to conduct clinical trials and make drugs available to patients. The mission of BioPontis Alliance is to bridge the gap between research results and *potential* therapies by generating a steady flow of well designed, developed and vetted *candidates*.

The development of effective treatments can be vastly improved by integrating patients meaningfully into the earliest stages of defining therapeutic objectives and relevant outcomes. This involvement should improve later experience in clinical trials, regulatory review and delivery of treatment to patients. Getting these and other factors more closely aligned, in collaboration between drug developers and patients with the targeted disease, and with clinical and basic science researchers, we believe should help to target the most meaningful health outcome improvements and avoid mistakes with clinical trial design (e.g., endpoints, biomarkers, and inclusion/exclusion criteria) as treatments enter human clinical trial studies.

The workshops and their output are the beginning of a new blueprint that we are co-creating with the community of patient organizations. The concepts and consensus on practical methods for integrating patients into drug discovery and preclinical development will next be implemented in specific drug discovery programs during 2017, in parallel with further exploration of additional improvements. Moving forward, the interests of regulators and future commercial partners who will bring candidate medicines through clinical trials and to the patients will also be explored in future conferences. The goal is to establish a new patient integrated continuum starting in pre clinical development then transferred to product development companies for the transition to clinical development, regulatory approval, and distribution to patients.