CLINICAL LEADER

The Vanguard of Patient Centricity: Patient-Led Clinical Trials

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Amid the AIDS epidemic during the late 80's, Dr Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, found himself at a crossroads. As a long-time proponent of the traditional "research to approval" drug development model, involving randomized clinical trials and lengthy regulatory reviews, Fauci was faced with the realization that this traditional approach would be of little benefit to AIDS patients without the luxury of time. Something had to be done. But what?

The breakthrough moment occurred during protests at the NIH campus in Bethesda, Maryland by highly motivated AIDS activists who were attempting to gain access to experimental drugs. As Fauci described years later,[1] "It was clear that something had to give, and at that moment that something had to be me." In a bold move to ease tensions, Fauci asked the police to stop making arrests and instead bring the protestors into his office to start a dialog. The interchange that ensued forced Fauci to confront the fact that new experimental drugs that had been deemed safe were not being given to those suffering from AIDS, but instead were being held back for additional studies to confirm efficacy. Numerous additional conversations with both patients and activists helped to drive home the reality of what those suffering from AIDS were dealing with, eventually causing Fauci to put aside conventional wisdom and change course. In the early summer of 1989, in one of the first examples of patient involvement affecting the course of the drug development process, Fauci openly called for a new Federal approach to AIDS research.[2]

Today patients are taking more responsibility for their own care as they mine the nearly infinite amount of data available on the internet. New technologies have enabled patients to become more connected and empowered, generate and share more data. Recognizing the opportunity to engage with highly motivated patients and/or patient organizations to both reduce cost and improve success in clinical trials, pharmaceutical companies are beginning to explore the concepts of patient-centric and patient-led clinical trials.[3,4,5]

Patient-Led and Patient-Centric Clinical Trials Defined

While today's technology-driven patients are having an impact on the way that clinical trials are conducted, there remains much confusion around terminology. This confusion flows from the fact that the movement towards greater patient involvement in medical care and research is not uniform across the industry. Many clinical trials are still conducted as they always have been, with all trial-related activities being controlled and organized by the sponsor or CRO, with very little, if any, opportunity for patient involvement or input.

Patient involvement in clinical trials can best be described as a continuum. At one end of the spectrum is patient-led clinical trials, in which patients take full ownership of all aspects of the investigation. In this case, patients take on all the responsibilities that normally fall on the study sponsor conducting the trail – recruitment, protocol development, data gathering and analysis.

As patient involvement decreases on the continuum is patient-centered research, where the existing research structure, with sponsors in charge and sites conducting the research, remains intact. Patient-centered clinical trials use the traditional randomized clinical trial (RCT) format, but engage with patients in order to more fully understand their needs, and/or to seek advice to help make the trial run more smoothly and efficiently, and ultimately more successfully.[1] In some cases, patients with the condition being studied are even brought into the process of conducting the trial - possibly helping to design the study protocol, determine the important research questions or outcome measurements, facilitate effective recruitment, etc.[6]

At the other end of the spectrum, with virtually no patient involvement, other than to serve as subjects of study, is the 'status quo' or traditional RCT. In order to avoid terminology confusion, it is important to note that the recently-popularized medical models of Precision Medicine or Personalized Medicine, which involve optimization of therapies based on analysis of a patient's unique characteristics, typically utilize the traditional RCT approach. Although these models are important developments in the effort to bring better and more effective care to patients, the main changes they bring are a more nuanced understanding of disease. As such, their practice does not require or often contain the enhanced patient involvement inherent in patient-led or patient-centered research.

Patient-Led Clinical Trials in Practice

In a recent survey of 273 senior executives from the life sciences sector, 53% of respondents revealed that becoming more patient-centered in their R&D strategy was a top priority, while nearly two-thirds of respondents indicated that their company had recently increased the level of funds expended on learning about patients.[7] One of the key drivers of industry efforts to increase patient-centeredness in clinical trials is the desire to demonstrate a medication's value to payers through its ability to contribute to the overall quality of life of patients. While pharmaceutical companies are clearly focused on incorporating aspects of patient-centeredness into clinical trials, fully patient-led trials are not currently a focus and have been rarely done inside the industry.

Despite this, several patient-led studies have been conducted to investigate a particularly devastating neurological condition is known as amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. In 2008, the first well-organized patient-led study was organized as a follow-up study to an encouraging Phase I trial conducted in Italy that treated subjects with lithium carbonate, which showed that lithium significantly slowed the progression of the disease. These results prompted patients on ALS discussion boards to organize a follow-up study to verify safety and efficacy. Some 350 ALS sufferers participated in the patient-led study that was organized online, with data being collected and analyzed in 3 month intervals with results posted on the project's website. Much to the dismay of the participants, reviews published at the 3 and 6 month intervals on the project website showed no significant evidence that lithium was effective in slowing the progression of ALS, prompting most participants to stop using the drug.[8]

Another prominent patient-led study currently being undertaken in Europe was organized by the AKU Society. Alkaptonuria (AKU) is a rare genetic metabolic disorder causing progressive arthritis of the spine and large joints. This patient-led effort is actually a series of 3 different studies designed to evaluate optimum dose, efficacy and the optimal age to begin treatment for the drug nitisinone.[9] In what may be an effective model for patient-led studies of the future, this patient-led effort utilizes partnerships with groups in industry (Sobi), patient organizations (AKU Society and ALCAP), hospitals (Royal Liverpool, Hospital Necker, and National Institute of Rheumatic Diseases), Academia (Universities of Liverpool and Siena, Institute of Molecular Physiology and Genetics) and Small and Medium Enterprises –SME– (Nordic Bioscience, PSR and Kudos). The key event which finally got this study off the ground after years of fundraising was a $6 million (Euros) grant from the European Commission.

The idea of patient-led trials is being to gain significant attention within the pharmaceutical industry with dedicated conferences[10] at which thought-leaders from across the industry gather to discuss how to collaborate with patients and patient groups for better trial outcomes.

Challenges of Patient-Led Clinical Trials

While patient-led clinical trials hold much promise for lowering costs and contributing valuable information to the drug development process, one of the biggest challenges inherent in patient-led trails is safety. If researchers and regulatory agencies cannot consistently predict if an experimental drug may cause a patient harm, how can we expect the patients themselves to effectively make this assessment? The DIY nature of patient-led trials can lead to increased risk for participants.

Another issue is bias. Patient-led trials are typically not randomized and have no placebo control. Instead of placebo groups, patient-led trials that utilize online data from patient groups found in organizations like PatientsLikeMe often use historical controls (outcomes of treated patients are compared with those found in the database who showed similar patterns of disease progression but have not been treated) which are not considered strong.6 Additionally, members of patient organizations like PatientsLikeMe may not be

representative of the general population. Paul Wicks, Vice President of PatientsLikeMe, noted, “when we’ve compared the PatientsLikeMe sample, for instance in multiple sclerosis, with a tertiary research centre in Boston that sees thousands of patients, we found the group of people who self-report and join PatientsLikeMe tend to be younger, are more likely to be female, and tend to be slightly better educated.”[11]

There are also several issues that tend to make pharmaceutical companies weary of patient-led trials. One example is that these types of unregulated activities may adversely affect company-initiated regulated drug development efforts already underway. Pharmaceutical companies are already struggling with the fact that only around 10% of novel treatments are eventually approved for market.[12] Given that patient-led trials can have safety issues, the fear is that if harm occurs in a patient-led trial, entire drug development programs could be forced to shut down based on results from one poorly controlled trial. Additionally, there is fear that patient self-experimentation may inhibit people from signing up for RCTs – why sign up for a trial where you might get a placebo if you can obtain the experimental drug on your own?

Finally, pharmaceutical companies face challenges in reaching out directly to patients. First, any contact a pharmaceutical company has with a patient needs to avoid undermining the doctor-patient relationship. Companies need to be clear with patients that the doctors provide the treatment for disease, and that they are simply interested in engaging with them to further research. It can be difficult for desperate patients not to see the pharmaceutical company as an alternative source of expertise, which may not exactly be viewed favorably by providers. Another issue is HIPAA privacy regulations involved in pharma-patient contact. In the above-cited survey, 43% cited uncertain regulatory requirements as a barrier to contact with patients.5

Conclusion

Pharmaceutical companies are beginning to understand the potential resource that exists in today’s motivated and disease educated patients to improve the drug development process. Efforts to advance a more patient-centered approach to clinical trials are well underway to tap this resource. The fact is that in today’s connected world, many patients understand their disease and needs better than their doctors or other medical professionals do. Typically, by acting through patient organizations and/or advocacy groups like: PatientsLikeMe, The Michael J. Fox Foundation for Parkinson’s Research, the AKU Society and more, patient-led clinical trials are starting to come online as part of the effort to speed development of new and effective medications.

While patient-led clinical trials are certainly an important contribution to the drug development process, they typically lack the controls and scientific rigor that are necessary for effective safety and efficacy analysis. Patient-led trials can provide valuable information that can be used to further research efforts, but they cannot and will not replace the Phase I - III RCTs that are necessary for full regulatory approval. Still, patient-led and patient-centered clinical trials are welcome additions to the ever-evolving drug development ecosystem that accelerates lifesaving medications to patients and challenges the ‘status quo’ in drug development processes.

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