Engaging the Patient's Perspective in Clinical Trials Research

Brooke Hefele[1], Sinéad M. Langan[2], Karen Pollins[3] and Joel M. Gelfand[4]

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INTRODUCTION

The first known human clinical trial was performed in 1747 by James Lind, when he treated 12 people suffering from scurvy with cider, vitriol, vinegar, seawater, garlic plus balsam of peru, or oranges plus lemons (Bartholomew, 2002). Since that time, dramatic advances have been made in clinical trials, statistical methodology, and operational strategies, with modern human studies often involving thousands of patients across the world. These trials have advanced scientific and medical knowledge dramatically from the use of citrus fruits to treat scurvy to the planning of trials to use genetically engineered T cells to treat pemphigus vulgaris (Ellebrecht et al., 2016). Despite these advances, clinical trials often suffer from poor enrollment, and in some cases poor design, which yield limited useful knowledge for key consumers of research findings: patients. Observational research has similar challenges, and the absence of patient involvement has been proposed as one of the factors contributing to focusing on lower priority research questions, which adds to research waste, using inappropriate outcome measures and poor interpretation, and dissemination of research findings. As a result, key stakeholders, including funding organizations, regulatory bodies, and patient organizations, are advocating for inclusion of patients in the research process from inception to dissemination of results (Kirwan et al., 2017). For example, the James Lind Alliance was established to bring patients, care takers, and clinicians together to prioritize unresolved questions about the effects of treatments (Chalmers and Glasziou, 2009).

IMPORTANCE OF THE PATIENT VOICE IN CLINICAL RESEARCH

Advances in medical care begin with research that emphasizes outcomes meaningful to patients (Selby et al., 2012). Too often, clinical studies culminate with a multitude of data, yet analyses and recommendations fail to fully translate into practice, leaving unmet needs for patients. Patient participation in all phases of the clinical research enterprise from identifying gaps in knowledge and setting research priorities to design of protocols and dissemination and application of the research findings in real-world settings is increasingly recognized as a vital component to generating data that promote positive changes in clinical practice (Barry and Edgman-Levitan, 2012). The Patient Centered Outcomes Research Institute's, which was established by the Patient Protection and Affordable Care Act, engagement rubric provides a foundation for researchers to apply greater involvement of and collaboration with patient partners (Figure 1) (Sheridan et al., 2017). In the United Kingdom, the INVOLVE initiative (https://www.invo.org.uk/) supports public involvement in all stages of research, including providing training and support for all stakeholders, and the King's fund provides practical suggestions for researchers and patients (https://www.kingsfund.org.uk/topics/patient-involvement).

NOTED OBSTACLES AND ISSUES

While patients have inherent knowledge of their experience with a disease, they may lack basic literacy in the myriad of issues relevant to human research. For example, in the United States, only 12% of adults have proficient health literacy skills (Kutner et al., 2006). This knowledge gap can lead patients engaged in research to feel intimidated, questioning their ability to add value to a study. Changing the culture of research is an ongoing process and can be met with resistance from professionals; encouraging investigators to take time to educate and train stakeholders, use plain language, and value their input enhances the impact of patient-oriented research (Carman and Workman, 2017). Additionally, the availability of participants varies and may often fall outside of the typical work hours for a research team, requiring flexibility from both patients and investigators. Of special importance is that patients from underrepresented communities may have distrust in the medical and scientific community, given prior ethical breaches, and therefore extra efforts need to be made to establish trust and create an inclusive environment (Corbie-Smith et al., 1999). Finally, the cost of attracting and retaining patient stakeholders can fluctuate, and requires flexible budgeting to account for unanticipated changes in patient engagement.

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[1]*Milken Institute School of Public Health, George Washington University, Washington, District of Columbia, USA;* [2]*Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK;* [3]*Jenkintown, Pennsylvania, USA; and* [4]*Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania, USA*

Correspondence: Joel M. Gelfand, Department of Dermatology, University of Pennsylvania, 3400 Civic Center Boulevard, Philadelphia, Pennsylvania 19104, USA. E-mail: Joel.Gelfand@pennmedicine.upenn.edu

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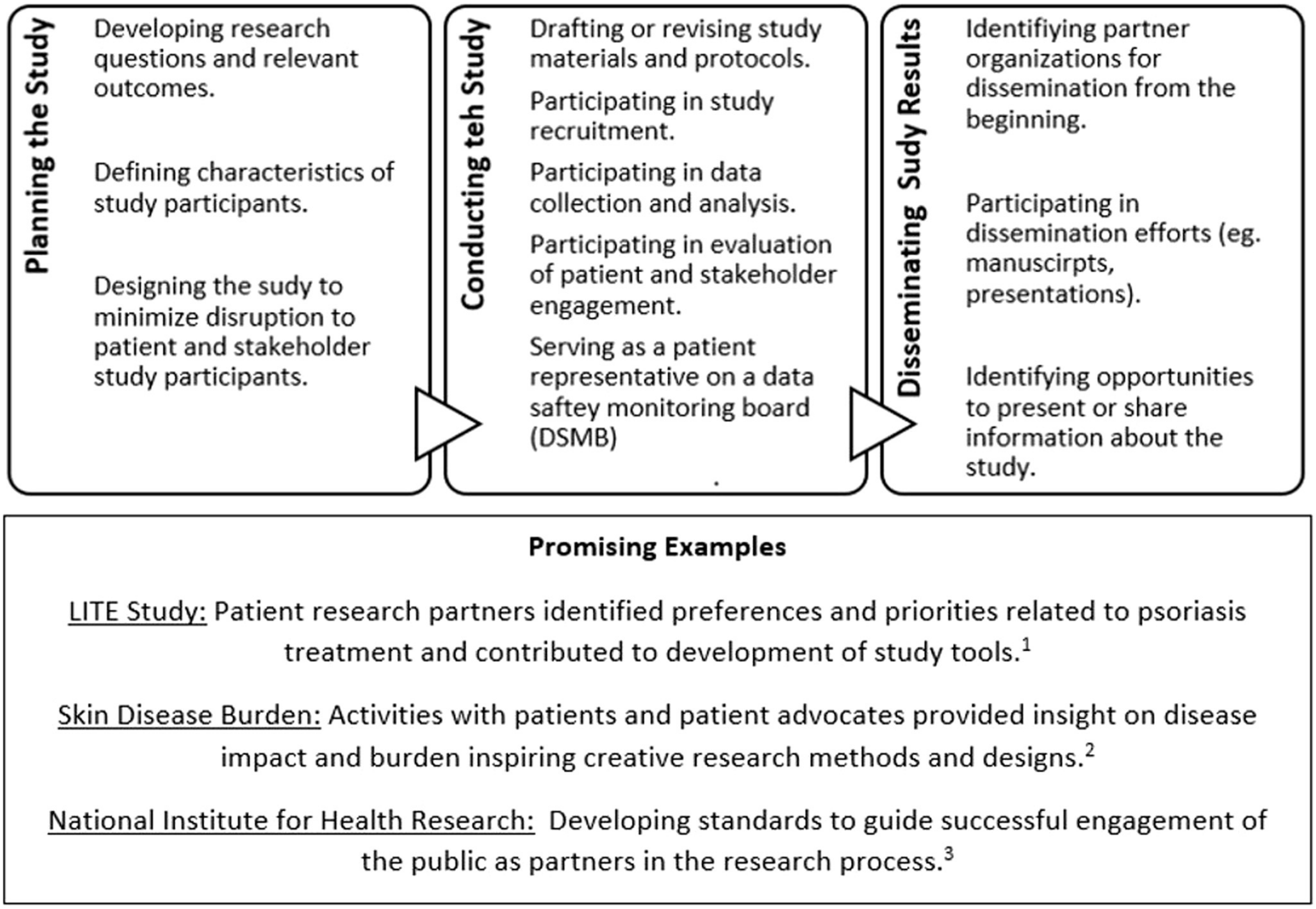

Planning the Study

Developing research questions and relevant outcomes.

Defining characteristics of study participants.

Designing the sudy to minimize disruption to patient and stakeholder study participants.

Conducting teh Study

Drafting or revising study materials and protocols.

Participating in study recruitment.

Participating in data collection and analysis.

Participating in evaluation of patient and stakeholder engagement.

Serving as a patient representative on a data saftey monitoring board (DSMB)

Disseminating Sudy Results

Identifiying partner organizations for dissemination from the beginning.

Participating in dissemination efforts (eg. manuscirpts, presentations).

Identifying opportunities to present or share information about the study.

Promising Examples

LITE Study: Patient research partners identified preferences and priorities related to psoriasis treatment and contributed to development of study tools.[1]

Skin Disease Burden: Activities with patients and patient advocates provided insight on disease impact and burden inspiring creative research methods and designs.[2]

National Institute for Health Research: Developing standards to guide successful engagement of the public as partners in the research process.[3]

Figure 1. Engagement rubric (adapted from Patient-Centered Outcomes Research Institute). [1]https://www.pcori.org/research-results/2017/pragmatic-trial-home-versus-office-based-narrowband-ultraviolet-b-phototherapy. [2]Bergstresser et al. (2012). [3]https://sites.google.com/nihr.ac.uk/pi-standards/home.

ENGAGEMENT STRATEGIES AND TOOLS

There are a variety of resources available to facilitate patient engagement in the research process, as described in Table 1. We encourage offering training and providing educational materials to participants in a manner that allows them to access as much information as is required, based on their individual learning needs without overwhelming or overburdening them with work. Of particular importance, incorporating visual aids and technology improves the understanding and recall of material for all types of learners (Kessels, 2003). This approach can be further enhanced through partnering with patient advocacy organizations, which often provide mentorship and other forms of support for their members who participate in research. Engaging partners through social media, websites, and apps draws a wider variety of participants inclusive of more diverse experiences and views. While in-person meetings are not always feasible, having at least one designated face-to-face conference boosts morale, entices further engagement and participation, and demonstrates to the patients their value and the importance of their contributions to research (see Figure 2). Setting clear expectations early on in the engagement process regarding the time commitment required and respecting patients' time ensures that meetings are not too frequent where participation lags, yet recurrent enough that patients do not lose interest or forget the progress already made. For example, our teleconference meeting schedule ranges from weekly during key study development periods, to monthly or quarterly, in order to maintain open lines of communication and progress. This approach can be supported with e-mail updates, detailed agendas, and recaps of conversations for the group to reflect upon when not directly engaged.

ILLUSTRATIVE EXAMPLES OF PATIENT ENGAGEMENT

We developed a pragmatic trial of home versus office-based phototherapy with patient engagement from inception. First, we conducted surveys of psoriasis patients across the United States to determine their priorities for comparative effectiveness research, while allowing for a broad representation of patients. We received responses from more than 1,400 psoriasis patients who are contacts of the National Psoriasis Foundation, which identified a strong preference for home phototherapy by patients as well as a strong priority of patients for comparative effectiveness research on this topic (Takeshita, 2013). We then reconfirmed these findings via Citizen Pscientist, an online patient engagement platform managed by the National Psoriasis

Table 1. Educational resources for engaging patients in clinical research

Resource	Overview	Access Point
Connecting Community to Research Toolkit	Downloadable toolkit to help deliver customized training in basic research methods and skills for community partners engaged in research projects.	http://sites.bu.edu/coeinwomenshealth/community/community-services/connecting-community-to-research/
CIRTification	Interactive human subject research training videos specifically designed in plain language for community partners and their unique roles in research. Trainings are available in English and Spanish.	http://www.ccts.uic.edu/content/cirtification
PCORI Methodology 101 Training for Patients and Stakeholders	Training booklet and resource guide for all stakeholders involved on research. Guides members in methodology, design, analysis, and interpretation.	https://www.pcori.org/sites/default/files/PCORI-Methodology-101-Training-Booklet-and-Resource-Guide.pdf
Research Fundamentals Workshop Series for Community Health Workers/Promoters	Workshop series and activity outline focusing on basic research concepts and fundamentals for community health workers and stakeholders in research.	https://actri.ucsd.edu/education/Documents/Workshop%20on%20Research%20for%20Community%20Health%20Workers.pdf
Introduction Partners in Research Community Scholars Training	Education for stakeholders and community partners involved in research. Provides definitions and guidance on engagement as well as outlines for recommended education based on circumstances.	https://hrpo.wustl.edu/wp-content/uploads/2015/04/2015-04-02v2-Community-Partner-Education-Manual.pdf
INVOLVE website and resources	Resource links for guidance in including the public in research. Combines expert knowledge and experience to advance inclusion by providing training tools, libraries, examples and community connections.	https://www.invo.org.uk/

Foundation (Afifi et al., 2017). A committee of five patients (one of whom, KP, is a co-author of this paper) informed the study design, outcome measurements, and application for funding. We intentionally limited the committee size as social science research generally suggests five to seven members are optimal for engagement. The patient committee members are diverse in age, duration of psoriasis, treatment experience, and skin type in order to reflect the study target population. Some patients were identified by the study principal investigator and co-principal investigator (both dermatologists) and others were nominated by National Psoriasis Foundation staff, thus ensuring inclusion of highly motivated patients who are have deep experience of living with psoriasis. The application, which detailed our plan

Figure 2. Stakeholders meeting for the LITE treatment effectiveness study. An in-person meeting of patient research partners and other stakeholders was held in September 2018 in order to achieve final input on the design of the LITE study. Patient input resulted in dropping one secondary end point in order to reduce burden to study subjects.

for patient engagement throughout the research process and a budget to support our patient research partners, was successfully approved in September 2017 (https://www.pcori.org/research-results/2017/pragmatic-trial-home-versus-office-based-narrowband-ultraviolet-b-phototherapy). The study will involve 1,050 patients stratified in thirds by skin type (type 1/2, type 3/4, and type 5/6). There will be two primary end points, one physician reported (clear or almost clear on a global assessment) and one patient reported (Dermatology Life Quality Index dichotomized to no to mild impact) with a non-inferiority margin of 15%. Our patient committee has telephone meetings on a weekly to monthly basis in the initial planning phases necessary to finalize the protocol; actively participated in an in-person stakeholders meeting in Philadelphia, PA in September 2018 (Figure 2); contributed to the development of the informed consent language and the testing of data collection tools; and selected the study acronym, LITE (LIght Treatment Effectiveness study). The patient committee will remain engaged in the study meeting on an approximately quarterly basis to provide feedback and will be involved in the interpretation and dissemination of results. Final decisions regarding study design, operations, and authorship are made by an executive committee that includes the study principal investigator and co-principal investigator (dermatologists), a biostatistician, a patient, and a National Psoriasis Foundation staff member (a patient advocacy organization). This organizational structure and our culture of mutual respect and shared decision making promotes active participation by patients. Similarly, patients have been key members of the UK Dermatology Clinical Trials Network since its inception in 2002 and have contributed actively to all aspects of the network from generating research ideas to interpreting and disseminating trial findings (http://www.bad.org.uk/healthcare-professionals/specialist-groups/uk-dermatology-clinical-trials-network).

CONCLUSIONS

The importance of the patient voice in clinical research is increasingly recognized by multiple stakeholders and in many instances is considered mandatory by funding organizations. Therefore, clinical scientists should develop expertise in effective methods to engage patient partners in the research process from the point of research prioritization through study design, execution, and dissemination of results.

ORCIDs

Brooke Hefele: https://orcid.org/0000-0001-8789-5377
Sinéad M. Langan: https://orcid.org/0000-0002-7022-7441
Karen Pollins: https://orcid.org/0000-0001-9508-3838
Joel M. Gelfand: https://orcid.org/0000-0003-3480-2661

CONFLICT OF INTEREST

Joel M. Gelfand served as a consultant for BMS, Boehringer Ingelheim, Janssen Biologics, Novartis Corp, UCB (DSMB), Sanofi, and Pfizer, receiving honoraria; and receives research grants (to the Trustees of the University of Pennsylvania) from AbbVie, Boehringer Ingelheim, Janssen, Novartis, Celgene, Ortho Dermatologics, and Pfizer; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly, Ortho Dermatologics, and Novartis. Joel M. Gelfand is a Deputy Editor for the *Journal of Investigative Dermatology* receiving honoraria from the Society for Investigative Dermatology. The remaining authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization of ideas: Brooke Hefele, Sinéad M. Langan, Karen Pollins, Joel M. Gelfand. Funding: Joel M. Gelfand. Investigation: Brooke Hefele, Sinéad M. Langan, Karen Pollins, and Joel M. Gelfand. Project administration: Brooke Hefele and Joel M. Gelfand. Resources: Joel M. Gelfand. Supervision: Joel M. Gelfand. Visualization: Brooke Hefele. Writing: Original draft—Brooke Hefele; review and editing—Joel M. Gelfand, Sinéad M. Langan, and Karen Pollins.

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