Integrating the Patient Perspective Into Research Design in the US:

Case Studies and Recommendations

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ABSTRACT

Clinical research—its methodologies, approaches, rigor, review processes, and results dissemination mechanisms—has resulted in tremendous benefits to both individuals and populations throughout its history in the US. Patients have traditionally played a subservient role in medical care—more or less willingly and by design—relying on an elite corps of educated experts to recommend and implement decisions. However, as the field of medicine advances into the 21st century, patients are called upon to make more, and more sophisticated, healthcare decisions with both financial and personal ramifications. As this trend has accelerated, it has become clear that the current state of clinical research has proven inadequate to serve the informational needs of this constituency, and new approaches have been proposed and tested, including those using uniquely 21st century tools, such as social media and ubiquitous technology.

While many of these efforts remain in their infancy, a review of several case studies can serve to illuminate trends and results, and enable recommendations and conclusions that can assist in the future of patient-centered research.

From this analysis, several major themes become apparent. First, the best patient-centered research directly assessed patient involvement using both qualitative and quantitative measures. Second, engagement between patients and a variety of stakeholders in the research definition process created synergies and insights that would not otherwise have revealed themselves, including a virtuous cycle that increased patient interest and involvement in general. Third, creating a systemic platform for on-going patient engagement can have long-lasting value through fundamental changes to the culture of research prioritization and design. These foundational benefits occur independently of the timing, nature and method of harnessing patient...
feedback, as well as the quantity of that feedback.

Patient-centered research, however, is still research and, as such, should function within the time-tested framework (ethical and otherwise) for conducting research. However, the evidentiary objectives of that research need to incorporate patient input in order to create a level playing field, and a common language, for the doctor-patient relationship.

Research that addresses these themes will enable patients to more readily participate in today’s healthcare system. Systemic participation will, moreover, provide value to the patient through collaboration with other stakeholders to identify optimal individualized care plans, make better informed decisions, and ultimately improve outcomes—all through focusing on the practicalities of the patient’s life and treatment journey.
INTRODUCTION

One need not conduct a literature review to readily identify treatments in popular US culture that have had a tremendous impact on societal health (think penicillin, the polio vaccine, etc.). Indeed, the evolution of clinical research from its early beginnings to the sophisticated machine we see today has been extraordinary, generating vast amounts of data, conclusions, and, yes, even more research questions. It has spawned an entire industry of conferences and publications that cater to both researchers and stakeholders such as payers, providers and policymakers.

Unfortunately, one stakeholder remains stubbornly outside of the research consumption paradigm: the patient. Simply put, patients are not “consumers” of research, they are “subjects” of research. While ethical and regulatory frameworks exist to legitimately protect patients who participate in research, patients do not typically help define either the inputs (research questions) or outputs (analysis and publications). And yet, patients retain a growing role in the details of their care, including the financial aspects of that care, and are therefore driven by necessity to understand the current state of the science around that care.

Three main imperatives underlie the growth of the need for a patient role—and, by extension, one for caregivers, support networks, and communities—in healthcare decision-making and the corresponding need for more and better information to assist in that decision-making.

1. Financial. As consumers are asked to pay more, and to pay a larger share, market forces will begin to shape decision-making and the need for greater transparency in the linkage between the evidence supporting the cost itemizations patients are receiving more often from providers. This decision-making will require more targeted and more relevant evidence uniquely suited to the patient. The best way to gather and present this evidence is to involve the patient in study planning and analysis. According to CMS (2013), out-
of-pocket healthcare expenses (i.e., those costs paid by the insured directly for their care) increased 3.2% between 2012 and 2013, after a 3.6% rise between 2011 and 2012. These expenses represent 12% of total healthcare spending. In addition, health insurance premiums (i.e., those costs paid by the insured to insurance companies) increased 2.8% between 2012 and 2013 after growing 4% rise between 2011 and 2012. This increase has been greater than the 1.7% and 1.5%, the 12-month inflation rate for January through December, 2012 and 2013, respectively (US Inflation Calculator, 2015). Overall, households contributed 28% of all healthcare spending (a percentage that has stayed steady since 2010), the largest share of all stakeholders ultimately responsible for healthcare expenses, a group which includes private businesses and federal, state, and local governments. Thus, as healthcare spending overall increased 3.6% in 2013 over 2012, the dollar amount individual consumers of healthcare expend has increased significantly in both nominal and real terms.

2. Cultural and technological. Typified by the rise of social media generally and also specifically the application of social media to the sharing of individual medical information, social media have allowed patients to connect with each other and share information, including research, as never before. This sharing, and the convenience and accessibility of the environment that enables it, have created an expectation on the part of the patient that they can and will be involved in research. According to its web site (PatientsLikeMe, 2015), PatientsLikeMe® has over 350,000 members sharing information on over 2,500 diseases and conditions. MediGuardSM, an on-line community of patients who participate in research and share information on conditions and treatments, has over 2.6 million members (MediGuard, 2015). Facebook®, moreover,
has 164 million daily active users in the US as of June, 2015 (Facebook, 2015), and it is rare to find a patient advocacy group that doesn’t have its own Facebook page, enabling information sharing across disease communities for patients.

The rise of social media and its application to patient-centric information sharing have created both a technological framework for sharing information about diseases and treatments, as well as an expectation that such information is merely a click away with brands that have built a trusted relationship with the member. Further, an important aspect of on-line patient communities manifests itself in the willingness of their members to participate in clinical research as well as their accessibility to would-be researchers.

Another example of a technological development linking patients to research takes the form of the Apple® ResearchKit for Developers (Apple, 2015), which enables the creation of apps that collect data (both user-entered as well as device-generated) for medical research, potentially enabling vast numbers of patients to participate in studies along with the collection of device-captured outcome data (e.g., heart rate) without the explicit need for clinical visits.

While cultural and technological developments such as these might a priori indicate an improvement in the patient-centric design of and accessibility to clinical research, much of these advancements have currently been leveraged only by traditional (i.e., non-patient-centric) research using patients as subjects in traditional research (albeit in novel ways, such as “crowdsourcing” data collection1). However, the distance between that

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1 The term “crowdsourcing” in the context of this paper refers to the collection of information—such as opinions, feedback, and actual data—from a large and presumably representative population cohort, in order to harness “the wisdom of crowds” as initially described by Surowiecki in his book of the same name (2015).
paradigm and true patient-centered research as illustrated in the below case studies is not
great, and this cultural/technological imperative certainly drives research closer to more
comprehensive patient involvement (Wicks, 2014).

3. **Structural.** An evolution of the basic tenets of the way healthcare is conceived and
delivered in the US represent a force necessitating a growth of the patient’s role in
research. Physicians themselves have begun to recognize the key part played by patients
through not only participation in, but also defining research. This recognition is in turn
driven by the need to discuss often complex elements of treatment and disease
collaboratively with patients when decisions are made. Tinetti and Basch (2013),
correctly state that in this context “To appropriately inform patient-centered decision
making, patient involvement is essential for identifying the questions to ask and the
outcomes to assess.” This viewpoint goes beyond the traditional call for patients to
participate as merely subjects in research, but to contribute substantively to research
design itself.

In addition, as the ultimate indication of the emerging impetus to involve the patient in
driving research, in 2010 Congress authorized the Patient-Centered Outcomes Research
Institute (PCORI), an independent nonprofit, nongovernmental organization charged with
improving the quality and relevance of evidence available to various stakeholders. The
PCORI approach, detailed in one of the case studies selected and presented below,
incorporates the patient perspective by design, attempting to address two primary
weaknesses in current research approaches: first, research doesn’t address the specific
concerns of patients and caregivers in the real world; and, second, existing research is not
typically available to those constituencies “in ways they can understand or use most
Below are presented 3 case studies of patient-centered research. In all three studies patients participated in the design of the research itself. Each case is described and then analyzed from a methodological perspective to draw conclusions as to the effectiveness of the approach taken with respect to incorporating the patient perspective into the design, analysis, and dissemination of the study results. Findings and recommendations from these analyses appear at the end of this paper.

**CASE STUDY 1: PROSTATE CANCER**

The first case study involves an explicit experiment to evaluate the utility and feasibility of stakeholder involvement in the protocol design for a cancer trial. The resulting manuscript, “Use of Crowdsourcing for Cancer Clinical Trial Development” (Leiter A, Sablinski T, Diefenbach M, Foster M, Greenberg A, Holland J, Oh WK, and Galsky MD, 2014) reveals a rigorous process for testing the impact of patient (and other stakeholder) involvement on both the process and the outcome of clinical trial design.

The general process followed for this study was as follows (Leiter A et al., 2014):

1. A Mount Sinai Genitourinary Oncology Research Team initially drafted a complete protocol;

2. A secure, web-based collaboration platform was made available (via electronic communication) to a group of clinical and research experts (through one author’s professional network as well as literature review), and also to prostate support groups (with a request to distribute to members), blogs, and prostate-cancer-related discussion groups on social-networking sites;
3. Both open-ended and closed-ended input was enabled for 6 weeks, after which point responses were categorized, analyzed, collated and presented to the Mount Sinai research team who drafted the protocol;

4. The results were evaluated and any modifications to the protocol were made by consensus of the Mount Sinai team; and,

5. Three independent reviewers assessed the protocol modifications to evaluate the results (and achieved sufficient consensus on the number of changes to validate the results).

The authors generously leveraged technology to enable this effort (Leiter A et al., 2014):

1. Electronic communication, such as email, to enable low-cost, high volume notification of the study;

2. Social media, to reach targeted groups of stakeholders likely to be interested and provide feedback; and,

3. A secure, web-based platform for managing collaboration and capturing feedback, as well as facilitating the collation of that feedback.

The authors agreed up front on two important and fundamental definitions. First, the concept of utility stratified into the implementation of major and minor changes. Major changes involved those to protocol elements including eligibility, dose, primary end-points, and the statistics plan. Minor changes represented all other changes. The threshold for achieving an acceptable utility of the feedback process required at least one major change or three minor changes to the protocol. In this way, the authors set a standard for the quality of stakeholder engagement.

Second, to qualify as “crowdsourced,” the effort to solicit feedback from stakeholders required at least 20 clinical/research experts and at least 20 patients (or their advocates). Given the wide
(and varied use) of the term “crowdsourced,” the inclusion of this definition indicates that the research team set clear objectives for the quantity of feedback that would be required to result in a useful process. Further, the numbers used indicate consideration by the team for the practicalities of the process: clearly the ability of a research team to integrate feedback (especially open-ended feedback, which has the potential to provide the greatest insight) is self-limiting. The researchers defended the limitation of the denominator as a) representing a significant interest over traditional practices with result to stakeholder (especially patient) collaboration and, b) enabling the type of open-ended feedback that results in so-called “gems” which drove protocol modifications (as opposed to simply enabling consensus that, while useful and confirmatory, did not drive process utility). The framework constructed by these two definitions provides a useful way of evaluating the results (Leiter A et al., 2014).

In reviewing the results of this effort, the authors focused not on the final study design itself, but, more relevantly to this analysis, on three areas of the process for soliciting input. First, the process did indeed result in a “crowdsourced” effort by the definition applied above, collecting feedback from 60 clinical/research experts and 42 patients (or their advocates). Second, with four major and five minor changes implemented by the Mount Sinai research team, the process met the utility threshold agreed upon prospectively by the authors. Finally, the authors solicited the opinion of the stakeholders with respect to the following statement: “I would participate in a similar clinical trial crowdsourcing effort in the future.” In response, 91% of the clinical/research experts and 76% of the patients (or their advocates) agreed or strongly agreed. Table 1 provides a sampling of the feedback provided by patients (or their advocates) and the changes made helps illuminate the value of this case study (Leiter A et al., 2014):
Table 1: Sample feedback from patients and their advocates and, where applicable, corresponding protocol modifications made by the Mount Sinai research team.

<table>
<thead>
<tr>
<th>Patient Suggestion</th>
<th>Protocol Modification (If Implemented)</th>
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<tbody>
<tr>
<td>“Provide interim and final results to all participants.”</td>
<td>Added secure website for patient access to real time results to protocol.</td>
</tr>
<tr>
<td>“Not having to travel long distances to participate.”</td>
<td></td>
</tr>
<tr>
<td>“Patients should discuss their experiences in taking metformin and whether it had any negative influence on their lifestyles.”</td>
<td>Added patient reported outcomes.</td>
</tr>
<tr>
<td>“I am always concerned about the risk for side effects and those are already detailed for the diabetic user and should cause a non diabetic (sic) equal concern.”</td>
<td></td>
</tr>
</tbody>
</table>

The authors discuss several limitations, both scientific (e.g., bias in the selection and participation of stakeholders) and practical (e.g., delays in trial development). Further, the authors, as expected, focus on the expandability and generalizability of the process, potentially to larger and larger groups of stakeholders (i.e., bigger “crowds”). However, in doing so, they demonstrate the potential to miss the value of patient engagement, which really occurs independently of the number of patients in the feedback cohort. In fact, in this case study a small number of feedback “gems” resulted in all of the protocol changes, dwarfing the value of
confirmatory feedback. Further, the term “crowdsourcing” is misleading in that it implies a linear relationship between the quantity and quality of interaction. Citing the work of James Surowiecki in *The Wisdom of Crowds* (2005), the authors imply that the main tenet of crowdsourcing—namely that the knowledge of a group can, under the right circumstances, be so great as to even exceed that of its smartest member—applies to clinical research design (Leiter A et al., 2014). Without debating the merits of this assertion, the results of this case study surely demonstrate the impact of patient stakeholder engagement on clinical design—and the value of this feedback both to the end result (i.e., the utility of the feedback) as well as stakeholder satisfaction—individually and generalizability. Indeed, it is likely that involving patients in study design at any scale will create a “virtuous cycle” that not only improves clinical research, but, in the vision of our next case study, also patient outcomes.

**CASE STUDY 2: UTERINE FIBROIDS**

A compelling case study in the involvement of patient stakeholders in research design appears in the form of a PCORI-sponsored project entitled: “Comparing Patient-Centered Outcomes after Treatment for Uterine Fibroids.” Part of what makes this case study unique and relevant to the concept of patient involvement in research design can be seen in the evaluation process through which it passed in order to receive funding.

The process for identifying potential PCORI research topics began with a rigorous evaluation at several levels. These levels included an evaluation by staff, outside experts, and a Science Oversight Committee and Advisory Panel; and included such criteria as: the type of research question (comparative effectiveness or not), the impact of condition on individuals and populations, the likelihood of findings to improve performance, and the topic’s inclusiveness across populations (PCORI, 2013). As a result of this initial process, uterine fibroids was
selected as a research topic, along with several others, including prevention of falls in the elderly and treatment options for severe asthma in African-Americans and Hispanic/Latinos (PCORI, 2013). Such purposeful patient-centeredness in topic selection highlights a strength of this case study.

Once the topic was identified, grant applications for specific research projects such as the one that resulted in this case study are evaluated based on, among others, a set of strict merit review criteria (PCORI, 2014):

1. Impact of the specific research question to be studied on the health of individuals and populations
2. Potential for the findings from the study to improve health care and outcomes
3. Technical merit
4. Patient-centeredness
5. Patient and stakeholder engagement

Criteria 1 and 2 simply extend the identified strengths of the research topic down to the level of the specific study, while criterion 3 is self-explanatory.

Criteria 4 and 5, however, drive much of the specific design elements in this case study and, as such, illustrate the power of patient involvement in study design.

Criterion 4, “patient-centeredness,” as a research descriptor, has a specific definition according to PCORI (2014), namely, such research must answer one or more of the following questions:

1. “Given my personal characteristics, conditions, and preferences, what should I expect will happen to me?”
2. “What are my options, and what are the potential benefits and harms of those options?”

3. “What can I do to improve the outcomes that are most important to me?”

4. “How can clinicians and the care delivery systems they work in help me make the best decisions about my health and health care?”

The proposal for this case study (Gliklich, 2013) states that question 1 will be addressed as follows:

With regard to the first question, the findings of this study will help women making decisions about different treatments for uterine fibroids understand how long they are likely to remain symptom-free following treatment and how personal characteristics, such as age and ethnicity, and disease characteristics, such as type of symptoms and severity of disease, are likely to affect their outcome.

Duration of symptom relief was selected based on a literature review of patient preferences, and the need for a follow-up procedure—especially a hysterectomy—was identified as a surrogate for that outcome in the datasets analyzed primarily also due to the aversion to such a procedure expressed in the literature among women experiencing uterine fibroids. Thus, documented patient input played a central role in outcome selection (Gliklich R, 2013).

The study design proposal also addressed question 2 “…by comparing both hysterectomy and surgical and interventional treatment alternatives.” According to the proposal, a review of the literature as well as prior experience with direct stakeholder engagement led to this choice of comparators. An excellent example of incorporating patient input into study design, that prior experience took the form of both an expert panel and a stakeholder committee represented by multiple stakeholder—including patients—which found primary interest in both the comparative
durability of alternatives to hysterectomy and, especially among women, the effects of uterine-sparing alternatives to hysterectomy on long-term symptom relief (Gliklich R, 2013).

Therefore, the study was envisioned “by design” to address one weakness of current research described above, namely identifying research questions of interest to patients (and, by extension, caregivers) through the selection of patient-centered outcomes and comparators.

However, the study also attempted to address the second weakness identified by PCORI: making the results of research available to patients and caregivers in an understandable way. With that in mind, the study designers specifically sought to engage stakeholders and patients, in accordance with criterion 5.

To meet this criterion, the proposal indicated that a panel of stakeholders, including patients, will be convened to review and provide feedback on the protocol and analytic plan for the study, with specific focus on the following: variable selection, subpopulation selection, data definition and presentation, analytic methods, and the process of interpretation of the analyses (Gliklich R, 2013). This list of elements was primarily driven by the study methodology itself, namely a retrospective observational study using secondary data sources (electronic medical records).

The implementation of this aspect of the study began with the selection of a Stakeholder Partnership Council (SPC) consisting of 17 individuals representing patients/consumers, payers, providers, and policymakers, selected based upon clinical expertise in uterine fibroid disease, experience supporting research and paying for treatments, and existing participation in patient advocacy activity (Meyers E, Messner D, and Velentgas P, 2014). The end result, currently anticipated for publication in late 2015/early 2016, will be a qualitative and semi-qualitative analysis of the engagement process by both investigators and the SPC, with an eye toward evaluating direct engagement measures such as trust, legitimacy, fairness, respect, accountability
and competence (Gliklich R, 2013).

While implementation of this aspect of the study is not complete, some initial results are available. Table 2 presents data on investigator consideration of an initial set of feedback from the SPC.

<table>
<thead>
<tr>
<th>Area</th>
<th>Number of Suggestions</th>
<th>Number Considered by Investigators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Follow-up</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Comparators</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Outcomes</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sub-populations</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>15</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2: Number of suggestions from the SPC considered by investigators by area of protocol and analysis plan

These data indicate a very small proportion of initial feedback from the SPC was considered by the investigators. While discouraging on the surface, the small number of suggestions considered likely resulted from several factors. First, the grant application for this study was approved by PCORI with many of the elements in the specified areas already defined, a necessary aspect of grant application submission. As such, flexibility post-award was likely
minimal. Second, many of the suggestions were not applicable based upon their dependence on earlier feedback, previously not considered. Finally, early engagement tends to generate a lot of feedback, likely in “brainstorm” mode. Data from subsequent, more focused, engagement sessions may well result in more relevant, useful, and, therefore, acceptable, feedback to the investigators.

In addition to discrete, study-by-study attempts to involve patient feedback in study design, some researchers have endeavored to create a systematic environment for continuously involving patients in research strategy and design elements. As our last case study demonstrates, the results can be cultural as well as scientific.

**CASE STUDY 3: OMERACT**

The Outcome Measures in Rheumatology (OMERACT) group meets biannually to define core outcome measures for rheumatic diseases based on international feedback. The group first included patient participants at the 2002 conference, its sixth, and has included them ever since. The conference organizer’s journey that led to this decision provides critical context for understanding the potential for integrating patient insight into the entire research culture when systematically sought.

Initially the OMERACT conference represented a collaboration of researchers focused on “the accuracy and responsiveness to change of clinically relevant (to patient and clinician) endpoints” in rheumatoid arthritis (RA) due to a lack of consistency in the application of—and the existence of a wide variety of—outcome measures (de Wit M, Abma T, Koelewijn-van Loon M, Colins S, Kirwan J, 2013).

Building on this initial success (the core set of outcome measures agreed upon by consensus at
the first conference was endorsed by the World Health Organization), the conference met every other year to continue to building similar consensus in other related disease areas. During the fifth conference in 2000, as the researchers explored patient reported outcomes (PROs), a “spontaneous” proposal, approved unanimously by the attendees, was made to invite 11 patients to the next conference in 2002 in order to incorporate their perspectives on the RA core set of outcome measures (de Wit M et al., 2013).

In 2010, a team attempted to qualitatively assess the benefits of patient involvement in study design (in this case, the outcome measures utilized) and the magnitude of that benefit. The assessment focused on 3 areas (de Wit M et al., 2013):

1. The research agenda;
2. The development of PROs; and,
3. The culture of the OMERACT conference, where research design occurs.

As explicit patient involvement in research decisions does not always get documented in literature, the method for conducting this assessment required innovative approaches. In addition to analyzing conference proceedings as published in the *Journal of Rheumatology*, the authors reviewed less formal correspondence (e.g., session reports, emails, invitations) related to the evolution of patient involvement, including arguments for and against and opinions expressed when such involvement occurred. A coding scheme was developed, which utilized 211 individual codes grouped into 27 categories to aggregate data based on descriptive characteristics of the content and the resulting analysis was utilized in a responsive evaluation in 2010 at the OMERACT conference in Malaysia (de Wit M et al., 2013).

The responsive evaluation took the form of qualitative interviews with a variety of stakeholders
using a hermeneutic approach. This approach seeks to interpret the meaning of social interactions (Little, 2008) and is frequently utilized in the social sciences. According to the study team, applying hermeneutic methods to the evaluation resulted in an ability to respect the plurality of opinions held by the various stakeholders, ensuring all perspectives were incorporated. Further, to reduce bias, two outside experts with no OMERACT affiliation were included in debriefings and methodological discussions (de Wit M et al., 2013).

Thirty-two semi-structured interviews were held, 16 of which involved patient participants, and topics included:

1. The expected role of patient participants;
2. Their selection, preparation and support; and
3. The expected or provided contribution to the OMERACT conference.

In order to incorporate a broad spectrum of views, interviewees were selected based on a stratified sampling methodology of conference attendees, focusing on four characteristics: stakeholder type, gender, geography of residence, the number of OMERACT conferences attended, and the “opinion about patient involvement” (as assessed by one or more of the authors). The authors attempted to dynamically balance the sample as views were expressed by participants in interviews and sampling ended when the authors agreed that saturation of views had been reached. Where possible, findings were cross-referenced in multiple sources, such as between documents and interviews, and personal recollections were included to fill any gaps (de Wit M et al., 2013).

The results of this analysis supported the value of patient involvement in the OMERACT conference. Based on structured interaction with patients at the first workshop in 2002, it
became clear that the perspectives of patients and researchers diverged with respect to outcome measures of importance in RA research. As a result, new studies in four topics (e.g., fatigue) were devised that questioned the perspectives of patients and incorporated outcomes of interest, such as foot problems and pain flares, into seven core measure sets, including fibromyalgia and gout. In addition, patient collaboration contributed directly to the creation of four specific new PROs, for example, measuring work productivity and pain flares. Patients also provided valuable input into assessments of the feasibility of outcome instruments and core measure sets (de Wit M et al., 2013).

The decision to integrate patients directly into the conference was an enlightened one, and one with unforeseen cultural consequences. Conference discussion, by nature, tends to be extremely collaborative and open-ended, with small groups focusing on a particular issue and then reporting back to the conference as a whole, either during the conference or later via the publication of proceedings. As such, the inclusion of patient perspectives in these discussions became part of the DNA of the conference implementation, establishing relationships and collaborations that resulted in an on-going platform for research design and prioritization. Patients became more than just consultants in OMERACT activities, but full collaborators and coauthors. In addition, the reliance on patients directly for feedback became the cultural norm for this group of researchers, further cementing the concept and creating synergies that extended beyond OMERACT as participants returned home and introduced patient perspectives into other research endeavors. For example, with input from OMERACT participants, the European League Against Rheumatism recommended that scientific projects involve patient representatives. A selection of quotes from conference participants illustrates this cultural evolution (de Wit M et al., 2013):
<table>
<thead>
<tr>
<th>Participant Initials</th>
<th>Quotation</th>
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<tbody>
<tr>
<td>RA</td>
<td>“Now what we have found is, and I changed my view, [be]cause it wasn’t only from OMERACT. As I got to know more and more patients, I realized, this sounds stupid because it’s so obvious but it wasn’t obvious to me, that a patient isn’t their disease. A patient is a person who happens to have a disease. What a big difference. Because if you’re a person that happens to have a disease, then for example you might have incredible skills in an area that might be very useful to move a clinical trial forward. So once I came to that realization then patient involvement becomes an absolutely obvious and integral part of moving forward.”</td>
</tr>
<tr>
<td>PM</td>
<td>“I can’t remember who brought up the subject, but someone mentioned fatigue. And that was the occasion when one of the other delegates said ‘well, everybody gets tired’. One patient shot to her feet and said ‘no, it’s not, it’s not like anything you’ve ever experienced; it’s not tiredness; it’s a complete wipe-out.’”</td>
</tr>
</tbody>
</table>
| RK                   | “Patients didn’t sometimes understand the objective of the research, which hindered us.”
“Patients were a kind of sparring partner when I entered a relatively new area. That was fun and did clarify a lot.” |
Table 3: Select OMERACT participant quotations concerning patient feedback

| RB | “I think, to be really honest, the patient involvement process in OMERACT and the changes in outcome measurements and the use of them in the drug tests has made a real difference for so many patients.” |

Admittedly the authors base much of their analysis on subjective criteria open to interpretation, despite the creation of a well-thought-through systematic framework for document review, a detailed methodology for participant interviews, and specific techniques to mitigate bias. The nature of the social trends being measured certainly do not lend themselves to the same rigorous scientific method as randomized controlled trials, and opinions can be as revealing as fact. However, the results clearly demonstrate the value of patient involvement, both in terms of the “talk” and the “walk” documented throughout the paper. More importantly, however, they describe the evolution of a complex system of stakeholder interaction in the crucible of a conference environment, and demonstrate both second- (i.e., cultural) and third- (i.e., network effects on other non-OMERACT projects) order benefits.
FINDINGS AND RECOMMENDATIONS

Each of the above case studies tackles patient engagement in slightly different ways, though all present useful lessons for future patient-centered research.

*Defining patient involvement in terms of quality and quantity objectives provides a useful yardstick*. By attaching numeric definitions and objectives to the size of the feedback cohort, as well as to the definition of feedback, researchers provide a useful and universal metric for comparing the degree of patient involvement in research design, which will further the interests of all stakeholder.

*Evaluate not just the outcomes of the process, but the process itself*. In addition to measures of participation, utility, and study design improvements, researchers should measure the satisfaction of those involved in providing feedback. As methods for soliciting, collating, evaluating and presenting the results of such feedback evolve, this information will help guide a more collaborative approach.

*While this paper focuses primarily on patient involvement, the synergies behind multi-stakeholder insight should not be ignored*. The interaction of perspectives, especially when those perspectives are freely shared via a robust technology platform across all collaborators, clinician and patient, creates the potential for new insights. In a very real sense, providing patient access to clinician feedback (and vice versa) can improve the quality of feedback from all.

*The relative merits of a curated list of stakeholder-contributors v. a mass audience have not been determined*. It is not clear that the use of a curated, finite list of stakeholder-contributors results in a qualitative difference in feedback, though certainly collating, evaluating and presenting
feedback from a mass audience presents practical problems that may result in a need to more strictly define feedback (i.e., to only closed-ended questions), thus reducing the quality of insights in favor of purely confirmatory feedback.

*Participation can be either direct or indirect.* The Uterine Fibroids case study illustrates this vividly, where study designers incorporated patient feedback indirectly from literature searches and previous, unrelated engagements, as well as through direct solicitation as part of the study. While results on the latter are still incomplete, early indications support the utility and power of indirect participation, especially where specific, detailed, documented information can be found in the literature. The practicalities of designing, evaluating, and funding research may drive investigators to the former.

*The timing of input matters.* Qualitatively, input during the conceptualization of the study likely has a greater impact than that solicited during protocol development and analysis plan finalization. While input at all phases is useful, the dependencies created during the study concept phase with future deliverables limits flexibility. The Uterine Fibroids case study supports this finding.

*A “patient-centric” framework for devising and evaluating research increases patient participation.* A framework such as the PCORI one described in the Uterine Fibroids study can play a significant role in systematically building in patient participation. For that case study, consideration of patient engagement and participation in the study design was “baked into” the funding proposal by necessity, resulting in a well-thought-through and multi-faceted approach.

*The types of patient engagement should be driven by the study design.* For the Uterine Fibroids case study, the retrospective database analysis drove the types of feedback patients could provide to the investigators (at all phases from conceptualization to analysis). In other types of studies,
involving patient communities, it is possible to involve patients in a variety of other aspects of research, including patient-reported-outcome instrument selection and data collection frequency.

While traditional statistical analysis may not be appropriate for evaluating the impact of patient involvement in study design, measure selection is important. On occasion, such as the evaluation of the value of engagement by the SPC in the Uterine Fibroids case study, quantitative analysis may not be called for. However, linking even qualitative analysis to key measures, such as trust and fairness, can significantly bolster the case for such engagement.

Research is a community endeavor, benefiting from standing communities of collaborators, including patients. The entire spectrum of activities involved in defining and conducting research can be seen as a complex system which benefits greatly when all stakeholders, including patients, are integrated into the culture of research, not just the process, via standing communities. Whether the community is virtual (i.e., on-line) or actual (i.e., a conference), the benefits are the same.

Patients hold different perspectives and priorities with respect to disease than other stakeholders, which can be both a benefit and a challenge. A certain amount of “curation” is necessary to prepare various stakeholders for collaboration, especially initial collaboration.

Patient contributions can be both subtle and surprising. de Wit et al., (2013) note in their discussion that patient feedback is valuable when it simply affirms what the researcher already believes, and also when, through dialog, it introduces new ideas, aspects, or elements that need further exploration. Further, it is sometimes difficult for researchers to distinguish between the two.
CONCLUSION

The premises and conclusions of this paper should be understood in the context of the many positive trends in the provision of healthcare in the US.

One important such development is the rapidly evolving area of personalized medicine. According to Chan and Ginsburg (2011), personalized medicine is “health care that is informed by each person’s unique clinical, genetic, genomic, and environmental information.” Many equate personalized medicine with so-called “precision-medicine,” but while personalized medicine enables “precision medicine” by the very nature of its personalization, “precision medicine” itself is best understood as an objective of personalized medicine. Chan and Ginsburg assert that a key element of personalized medicine, clinical decision support (CDS), for both patients and clinicians is necessary to reach the goal of personalized medicine, namely “…to optimize medical care and outcomes for each individual, resulting in an unprecedented customization of patient care” (Chan I and Ginsburg G, 2011). Reaching this goal therefore requires better and more accessible evidence for the patient in support of CDS.

The on-going and intense focus on improving the quality of the US healthcare system, as measured by six proposed aims—safety, effectiveness, patient-centeredness, timeliness, efficiency, and equality—has highlighted the need to focus on the patient. This landmark report, Crossing the Quality Chasm, specifically calls for considering and respecting the needs, preferences, and values of patients in clinical decision-making (Committee on Quality of Health Care in America, 2001). However, as the application of the important principles presented in that report evolve to meet today’s challenges, the ability of patients to understand and express needs, preferences and values in the language of clinical decision-making (i.e., evidence) requires that patients play a larger role in defining the research that supports this decision-
making.

Additionally, the Institute of Medicine has extended its focus on quality to also identify ways to improve the value of healthcare. One concept at the heart of their recommendations takes the form of a “continuously learning health system,” where patients and clinicians form partnerships in the provision of care based upon shared science, information, incentives and, ultimately, a culture of continuous improvement (Smith M, Saunders R, Stuckhardt L, McGinnis JM, 2013). The concepts and ideas presented in this paper lend support to—and are, in turn, directly supported by—their conclusions.

There are, however, challenges with empowering patients to act beyond the clinical research framework as detailed by Wicks and Vaughan (2014). A well-known study initiated by patients and caregivers using the “Patients Like Me” platform led to a rise in the off-label use of lithium carbonate to treat amyotrophic lateral sclerosis (ALS) after several patients utilized Google translate to access a paper suggesting it might slow their illness. It was unclear where, if any, ethical oversight lay and lithium carbonate was later found to be ineffective. Further, patients enrolled in clinical trials for two ALS treatments “broke the blind” and shared data on-line. Not only did this undermine the research, but led inadvertently to a group of unenrolled patients ingesting the industrial cleaner sodium chlorite which was suspected to be the active ingredient in one of the drugs in the trial. These patients progressed worse than expected (Wicks P and Vaughan T, 2014).

These trends and challenges highlight the dissonance caused by an imbalance in the quantity and quality of information retained by providers when compared to patients. As such, it is necessary not to discard the existing clinical trial framework, but simply to rebalance it so that all stakeholders, including patients, can contribute equally and on the same level playing field using
the language of evidence.

In conclusion, the role of the patient in clinical research continues to increase in importance as the complex system that is medical care evolves. A key element of that system, the research agenda and those who maintain and implement it, can certainly benefit from more patient involvement. This collaboration can take many forms and is multi-faceted in the value it provides, including identifying optimal individualized care plans, making better informed decisions, and ultimately improving outcomes. When implemented and measured properly, it encourages participation in research and improves the relevance to both patients and other stakeholders by incorporating the practicalities of the patient’s life and treatment journey into evidence generation. When implemented systematically, it holds the potential to reshape both the culture of research and the relationships between patient, provider, payer and policymaker, leading to improved clinical outcomes.
REFERENCES


