Patient Engagement at a Tipping Point—
The Need for Cultural Change Across
Patient, Sponsor, and Regulator
Stakeholders: Insights From the DIA
Conference, “Patient Engagement in Benefit
Risk Assessment Throughout the Life Cycle
of Medical Products”

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Abstract
Benefit-risk assessment is the foundation for decision making throughout the life cycle of medical products. Because patients are
the beneficiaries of the efficacy of medical treatments and also bear their possible risks, their perspectives and judgments about
value and the relative importance of benefits and risks should be at the heart of the medical decision-making process. Patient
engagement is now at a tipping point; there have been a growing number of patient engagement initiatives over the past several
years, but there remains the need for a common language, alignment on engagement approaches and best practices, and a shared
vision regarding a desired future state. This article discusses insights gleaned from the DIA conference, “Patient Engagement in
Benefit-Risk Assessment throughout the Life Cycle of Medical Products” (September 2015). It highlights the changes that will need
to occur within the patient, medical-product sponsor, and regulatory cultures in order for patient engagement to become
integrated into the medical-product development process and life cycle maintenance. Furthermore, it emphasizes that reaching
the desired future state will require a conscious commitment from all stakeholders to work collaboratively to develop shared
solutions and to map a common path forward.

Keywords
patient engagement, patient perspective, benefit-risk, medical decision making, drug development, patient outcomes

Introduction
Benefit-risk assessment is the foundation for decision making
through the life cycle of medical products.1 Evaluating the
benefits and risks of a medical product involves both technical
assessment of the scientific evidence as well as societal value
 judgments about the importance of its benefits and risks. To
date, regulators and medical-product sponsors have rendered
those value judgments almost exclusively. Increasingly, how-
ever, the patient’s perspective is recognized as being of equal,
if not paramount, importance in this regard. This critical shift
stems from the view that since patients are not only the bene-
ficiaries of the efficacy of medical products but also bear their
possible risks, their perspectives and judgments about value
and the relative importance of benefits and risks should be at
the heart of the process.

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The issue of patient engagement in the benefit-risk assessment of medical products was the subject of a recent conference, “Patient Engagement in Benefit-Risk Assessment throughout the Life Cycle of Medical Products,” which occurred on September 16-18, 2015, in Bethesda, Maryland. Hosted by the Drug Information Association (DIA) and partially funded by the Patient-Centered Outcomes Research Institute (PCORI), it brought together an engaged group of stakeholders, including patient partners, regulators, and medical-product sponsors and academic researchers to discuss the current and future states of patient engagement in benefit risk assessment through the medical product life cycle.

The conference summary, including key learnings, can be found on the DIA website (http://www.diaglobal.org/en/resources/tools-and-downloads#Visual-Model). This article discusses key insights gleaned from the DIA conference and highlights the changes that need to occur within the cultures of patient partners, medical-product sponsors, and regulators to achieve meaningful integration of patient perspectives in medical benefit-risk assessments. In doing so, it builds upon existing guidelines and literature on patient engagement practices in clinical trials and translational research developed by PCORI, the Clinical Trials Transformation Initiative (CTTI), and the National Institutes of Health (NIH).

Cultural Change Among Patient Partners

The vision of the health care system of the future is one of a “continuous learning system” in which patients play a central role, actively partnering with health care professionals to improve the safety and efficiency of health care delivery as well as the effectiveness of health care outcomes. Fulfillment of this vision will require a transformation in how patients view themselves and their role in the health care process. Specifically, in the health care system of the future, patients will need to possess “the motivation, knowledge, skills, and confidence to make effective decisions to manage their health.” Importantly, these attributes and skills apply not only to the patient’s role within the health care system as a whole but also to his or her role within the more focused context of the medical-product development process itself.

At the present time, however, there are several barriers that can potentially impede this transformation. A first and fundamental barrier is the fact that many adults struggle with health literacy: that is, they lack (or are deficient in) the ability to “obtain, process, and understand basic health information and services,” skills that are essential for shared health decision making. In recognition of this gap, there has been a call for health care institutions to become “health literate”: that is, to become organizations “that support people as they navigate, understand, and use information and services to take care of their health.” By extension, it behooves medical-product sponsors and regulators to become health literate entities as well. Being health literate entities involves taking steps to ensure that all patient-directed materials (print, digital, etc) are comprehensible and actionable for patients of all literacy levels. Similarly, it involves offering training and educational opportunities for patients to assist them in improving their level of health literacy and in learning how to engage effectively with health care professionals, medical-product sponsors, regulators, and other relevant parties. Moving forward, both sponsors and regulators should consider the application of health-literacy principles when designing product benefit-risk information for patients, and they should consider developing and publishing performance metrics on their progress in doing so. Similarly, patient-advocacy groups should also consider advocating for the application of health-literacy principles in the development of patient educational materials, and for standard-setting for high-quality health education materials.

A second barrier is intrinsic to the current health care process itself. Patients are but a single component in a highly complex and fragmented system. If patients are to assume a more engaged role and share in medical decision making, health care professionals, payers, and administrators will need to value patients as partners in the health care delivery process. Equally important, however, is that patients have the opportunity to gain proficiency in shared decision-making methods. Decision-support tools, such as those featured in the Agency for Health Care Quality’s shared decision-making toolkit, can be an effective way to introduce key concepts (eg, benefits, risks, uncertainties, and benefit-risk balance) and to train patients in using a structured, systematic approach to reaching a decision. Importantly, decision aids can be tailored to be sensitive to cultural differences as well as other factors that can affect decision making (eg, age, stage of illness).

Within the drug development arena, patient advocacy groups can reinforce the notion of patients as valued partners by demanding meaningful engagement opportunities for patients (as opposed to token or “symbolic” efforts). Similarly, sponsors and regulators could consider developing and publishing metrics on their efforts to engage patients and to incorporate the patient perspective. They might also consider using a structured framework to help guide and facilitate “meaningful patient engagement,” one which specifies where, when, and how patients should be involved in the drug development process. Patients can contribute to the development of such a framework, particularly in terms of delineating patient engagement venues (eg, committee membership, focus groups, clinical trials, advisory boards) and scope of patient responsibilities (eg, as consultant, decision maker, respondent).

Patients will also need training in the drug development process itself. Training topics might include, for example, the drug development life cycle, clinical trial design, how to critically appraise clinical trial data, and how to evaluate the benefits, risks, and uncertainties associated with medical products. The training curriculum offered by the European Patients’ Academy on Therapeutic Innovation (EUPATI) is a useful model in this regard. Informal caregivers (eg, parents or other family members, close friends) should be offered training and...
opportunities for engagement as well. Engaging informal caregivers is particularly important in instances where the medical condition affects infants, young children, or the elderly. In such cases, the informal caregiver’s perspective may be the only way to gain insight into patient preferences for treatment. Such surrogate viewpoints can provide important perspectives regarding relevant clinical trial endpoints.

Cultural change among patients, while necessary, cannot occur within a vacuum. Change within the patient culture will require commensurate change within the health care system structure, and in the awareness, attitudes, and behaviors of the health care providers, payers, and administrators who work within it. Examples of pertinent health care system–level change initiatives include modifying clinical practice guidelines to specify decision points where patient involvement should be elicited, training health care providers on patient-engagement methods, and ensuring that health savings accounts and state health insurance exchanges involve patients in meaningful ways. Specific initiatives that can support and/or accelerate patient cultural change in terms of the medical–product development process per se include promulgating standards for benefit-risk communication in product-labeling materials, incorporating patient-reported outcomes data in product labels, and including endpoints in clinical trials that patients themselves have identified as being meaningful and which adequately reflect the spectrum of the disease experience and the diversity of the target patient population.

**Cultural Change Among Medical-Product Sponsors**

Cultural change is already underway within medical-product sponsors. This can be seen, for example, in the fact that individuals who participate in clinical trials increasingly are seen as patients, volunteers, and even collaborators, rather than as “study subjects” or “customers.” The assumption that a few patients could adequately represent the diversity of an entire patient population is giving way to a more realistic view that acknowledges the heterogeneity of experiences and values within patient populations. Sponsors are also creating “chief engagement officers” and other patient-engagement leadership roles, reflecting meaningful commitment in this direction.

Numerous other cultural changes still need to occur, however. Viewing patient involvement as beneficial, rather than as a challenge to the benefit-risk assessment process, is one key step in this direction, as it can foster strong collaborations or “working partnerships” between sponsors and patients.16,17

Close, proactive partnering with patients will enable sponsors to ensure that they are indeed measuring clinical outcomes and other attributes (eg, convenience) that are relevant to the target patient population. Such partnering can be facilitated by the use of established techniques including, for example, direct-to-consumer advertising approaches and patient-targeted labeling. However, sponsors should also consider facilitating the partnering process through other means as well. For example, one important partnership-building activity is for sponsors to collect data firsthand from patients regarding their experience living with their disease or medical condition, including both aspects of their disease and treatments that they find to be most difficult or challenging as well as outcomes that they value most in their daily lives. Patient testimony at a US Food and Drug Administration (FDA) advisory committee meeting for an oncolytic viral therapy proved to be a key factor in convincing the Agency to accept a novel primary endpoint (lesion shrinkage) as clinically meaningful, despite the absence of positive overall survival data, thus opening the way for full approval of the product.18 This example underscores the growing recognition of the value of patient input and an openness to include it in drug development and regulatory approval.

Sponsors should also consider partnering with patients to develop structured patient preference instruments. These instruments can quantify how patients value clinical outcomes and other aspects of treatment (eg, dosing administration options), as well as the benefit-risk tradeoffs that they would accept. In addition, once a medical product is approved, sponsors need to provide information that facilitates both public health and individual patient decision making. Such information must not only be transparent but reflective of the concerns and interests of patients, and it should be presented in a manner that is understandable to patients. Patient preference studies support these objectives.

To date, companies have typically sought patient input late in the drug development process, for example, when they have identified a gap in their development program data that may affect regulatory approval. Ideally, going forward, companies would establish a framework for patient involvement that specifies that patient engagement begins early in the drug development life cycle. Both patients and sponsors would benefit from earlier, and ongoing, engagement. Workable solutions for sponsor concerns such as intellectual property and perceptions of off-label promotion need to be identified to enable the establishment of such a patient engagement framework.

There are inherent conflicts within medical product development related to stakeholders’ disparate goals. Sponsors seek to develop novel treatments that are safe and effective for patients. To do this, they generate evidence for regulatory authorities and payers to gain marketing authorization and reimbursement approvals, respectively. When designing clinical trials, sponsors seek to narrow the patient population being studied to identify the relevant patient populations that are most likely to benefit from the treatment and to control for heterogeneity in order to demonstrate efficacy. They also seek to show clinical differentiation from available therapies to provide evidence of cost-effectiveness.

Moving forward, in addition to clinical and demographic variables, sponsors should consider conducting subgroup analyses based on specific patient values and experiences as well, for example, patients’ willingness to pursue more aggressive treatments earlier in the course of their disease. Doing so, however, may introduce new challenges in the need for novel
design and analysis of clinical trials. If larger sample sizes are needed to ensure greater heterogeneity in some circumstances, additional data collection and analysis requirements could add to the financial risk of clinical trials and hence may delay efforts to deliver medicines sooner. In this area, the partnership between medical-product sponsors and patients in defining the most important research questions is important, allowing design of appropriate data collection and analyses for the benefit of the patients who need the therapy.

Patient partners, on the other hand, need information to help them decide whether a medical product would be appropriate in their own circumstances. In light of the different perspectives between medical-product sponsors and patients, it is encouraging that sponsors and other stakeholders are increasingly heeding the call to action for progress toward a universal “framework” in which to engage patients in drug development.10

There are clear opportunities for medical-product sponsors to strengthen their relationships with other stakeholders to develop shared solutions to patient engagement. For example, with patient advocacy groups becoming more organized and attuned to the science of drug development, sponsors have an unprecedented opportunity to engage with patient partners in this way. There is also the prospect for sponsors to deepen their partnerships with regulators, as highlighted by the keynote address from the FDA’s Deputy Commissioner (now Commissioner), Dr Robert Califf, at the DIA conference. Dr Califf spoke about his early clinical trial work, which involved asking patients for clarity on the tradeoffs they were willing to make in their medical treatment. From this experience grew his appreciation of the value of patients’ perspectives. His keynote address underscored that patient preferences and perspectives are important to the FDA.20

Cultural Change Among Regulators

The regulatory culture has changed dramatically in regard to patient engagement over the past century. Historically, regulatory communications and other interactions were focused exclusively on health care providers rather than patients. In 1938, for example, a Federal Register notice stated that drug labeling should be written “only in such medical terms as are not likely to be understood by the ordinary individual.”21 It was not until 1970 that the FDA mandated that benefits and risks of medical products be provided directly to patients.21 Since then, regulatory authority policy changes have moved patient engagement from the involvement of one “expert” patient to inclusion of multiple patient voices along the spectrum of care.22

Both the FDA Safety and Innovation Act (FDASIA) of 2012,23 which mandated the inclusion of patients in the drug development process, as well as the more recent Patient-Focused Drug Development meetings hosted by the FDA,22 represent major milestones in the FDA’s shift toward greater patient engagement. FDA’s devices division likewise provided draft guidance recently to explain the principal concepts that sponsors and other stakeholders should consider when choosing to collect patient preference information, and to provide recommendations on how patient preference information should be incorporated into device labeling for patients and health care professionals.24 Pharmacovigilance legislation passed in 2010 in the European Union also mandated greater transparency, communication, and patient involvement in drug development.25 Additionally, the European Medicines Agency (EMA) recently revised their framework for interacting with patients and consumers to better incorporate those stakeholders’ values and preferences in regulatory decision making.26 Encompassing patient participation, consultation, and information, the framework obligates specified EMA scientific committees to take into consideration the input of the agency’s stakeholders, including patient and consumer organizations.27

Numerous ongoing developments28 also are shaping regulatory policy in this regard. Examples include ongoing work by the International Conference on Harmonisation to incorporate aspects of structured benefit-risk assessment—including patient-preference data—in the Common Technical Document for regulatory submissions,29 and the release of a catalogue of patient preferences research methods by the Medical Device Innovation Consortium,30 a non-profit organization that operates in partnership with the FDA to advance medical device regulatory science. It is notable that the proposed 21st Century Cures Act is also anticipated to require incorporating data gleaned from patient engagement into regulatory decision making.31

Many regulatory efforts still are in the pilot stage, and it is unclear how they can be scaled to deliver useful information about patient preferences across the full range of illnesses and treatments. To advance in this regard, there is a need to clarify not only how to collect and incorporate patient engagement information into regulatory decision making, but also at what points it would be most useful to collect such information during the drug development life cycle. Additionally, there is a need for approaches to resolve potential methodological, legal, and ethical concerns relating to patient engagement. For example, to assess the likely benefit from product exposure, regulators would need to extrapolate from pre-market data to the post-market setting the proportion of a patient population for whom perceived benefits would exceed the risks of a medical product. Similarly, regulators would need to determine how to assess and account for differences in preferences across various stakeholder groups (eg, patients, caregivers, and caretakers) and account for this in a label.

Looking to the future, the regulatory culture will need to continue to evolve, particularly in the following ways. First, regulators should encourage development of patient engagement and patient preference elicitation as scientific fields subject to widely accepted standards for evidence. Regulators also should continue to engage with the wider scientific and industry communities to identify rigorous approaches for providing quantitative evidence on patients’ preferences and to provide
To tailor medical products for individual patients, pervasive deficits in health literacy skills, a shortage of venues for patient participation in the medical product-development process, and a lack of meaningful opportunities for patient engagement in the medical product-development process create barriers to patient engagement. In this vein, regulators can also look to the PCORI, CTTI, and NIH best practices for guidance on scientifically defensible approaches to collecting and using both qualitative and quantitative data. To meet these challenges, it is vital to develop a framework that describes when and how to engage patients, and how to minimize barriers for patient engagement. This framework should allow for collaboration with medical-product sponsors to develop a framework that delineates substantive roles for patients and appropriate patient engagement venues.

Although regulatory benefit-risk decisions have, by definition, always been made under conditions of uncertainty, there is ongoing debate regarding the level of remaining uncertainty that is acceptable before a particular regulatory decision can proceed. Part of this uncertainty relates to the degree and type of risks that are tolerable in the context of a particular medical product’s benefits in the intended patient population. Expanding the patient’s role in regulatory benefit-risk decision making via “the more thoughtful identification and compassionate use of the individual patients’ predicaments, rights, and preferences in making clinical decisions about their care,” can help to reduce this uncertainty and, moreover, is consistent with the premise of evidence-based medicine. In this vein, informing regulatory decisions with knowledge of patients’ risk tolerances would constitute a significant advance over the current practice of exclusive reliance on regulators’ own risk tolerances.

### Table 1. Barriers to Cultural Change and Proposals to Address Barriers Among Patient Partners Relating to Patient Engagement in Medical-Product Development.

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<thead>
<tr>
<th>Barriers to Cultural Change</th>
<th>Proposals to Address Barriers</th>
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<tr>
<td>• Socialized to defer to health care providers in medical decision making</td>
<td>• Educate regarding the value of shared decision making</td>
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<tr>
<td>• Lack of training in shared decision making</td>
<td>• Embed the use of shared decision-making support tools (eg, from the Agency for Healthcare Research and Quality) within the health care delivery process to support patients in shared decision making</td>
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<tr>
<td>• Pervasive deficits in health literacy skills</td>
<td>• Implement a “health literate” approach in patient care processes</td>
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<tr>
<td>• Lack of meaningful opportunities for patient engagement in the medical product-development process</td>
<td>• Apply health literacy principles in the development of patient-directed materials</td>
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<tr>
<td>• A shortage of venues for patient participation in the medical product-development process</td>
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<td><strong>Healthcare system:</strong></td>
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<td><strong>Patient advocacy organizations:</strong></td>
<td><strong>Proposals to Address Barriers</strong></td>
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<tr>
<td>• Demand meaningful engagement opportunities for patients in the medical-product development process</td>
<td>• Collaborate with medical-product sponsors to develop a framework for patient engagement that delineates:</td>
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<td></td>
<td>• Substantive roles for patients, and</td>
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<td>• Appropriate patient engagement venues</td>
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strategies, for example, in the case of teratogenic risk, consider-
ing and designing appropriate programs to ensure adequate informed consent, and use of contraception should the medicine be deemed to have an appropriate level of benefit to justify this risk.

**Reaching the Future State as Partners**

Patient engagement in medical-product development cannot advance without substantial cultural changes from all stakeholders, including patient partners (Table 1), medical-product sponsors (Table 2), and regulators (Table 3). Patient engagement is now at a tipping point; while the number of patient-engagement initiatives has been increasing over the past several years, there remains the need for a common language, alignment on engagement approaches and best practices, and a shared vision regarding the desired future state. In addition, medical decision making will need to incorporate the values and preferences of patients and caregivers, and patients will need to be empowered to participate more fully in the process. Not least, there must be alignment among stakeholders regarding when and how to engage patients in medical-product development. Achievement of this envisioned future state will require a conscious commitment from all stakeholders to collaborate in developing common solutions and in mapping a common path forward.
**Author Note**

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**Notes**

1. For the purposes of this article, the term medical product (or product) refers to drugs, biologics, and/or devices.
2. Patients, according to PCORI, are persons with current or past experience of illness or injury (http://www.pcori.org/funding-opportunities/what-we-mean-engagement/pCORis-stakeholders). Because of the diversity of patients, there is often no “average patient.”
3. The term patient partners includes patients as well as their family members, caregivers, and the organizations that represent them (http://www.pcori.org/funding-opportunities/what-we-mean-engagement).

**References**


