

Regulatory decision-making meets the real world

Ryan Hohman, Michael Shea, Marina Kozak, Samantha Roberts, Jeff Allen, Ellen Sigal*

As patient input in drug development increases and new data sources are tapped, regulators need to organize and ensure the quality of data to inform decision-making.

Over the past several years a diverse set of stakeholders representing government, academia, industry, and patient advocacy has collaborated to streamline the drug development process. Guidelines have been established for the codvelopment of targeted drugs and companion diagnostics so that testing procedures are in place as soon as a new drug is approved. The concept of umbrella and basket clinical trials has been put into practice to study multiple drugs at once, avoiding waste created by duplicative research. Regulators have implemented programs to provide advice and feedback to drug developers early in the development process to guarantee sound data collection and to ensure that the review process is not slowed down by missing information.

These ongoing efforts will likely soon be coupled with additional initiatives stemming from activities in Congress aimed at accelerating the pace of medical discoveries. Central to these legislative proposals are provisions to facilitate the collection and use of two important types of data to aid in regulatory decisions: “patient experience” and “real-world” data. We are now entering an era of patient-centeredness and big data, where patients are no longer “passengers” but instead are “co-pilots” (1), and information generated from the practice of medicine is produced in real time. These two movements pose opportunities to improve health care, as well as inherent challenges in discovering the optimal way to quantify and include the patient experience in regulatory decision-making and making smart use of real-world data to bolster what is known about new treatments.

At a recent Friends of Cancer Research roundtable with Dr. Robert Califf of the U.S. Food and Drug Administration (FDA), stakeholders met to discuss patient input

and regulatory innovation. We summarize here the thoughts and recommendations for enhancing the use of patient-centered data in regulatory decision-making.

GAINING EXPERIENCE DATA

Patient experience data include data collected by patients, caregivers, and patient advocacy organizations, among others, that are intended either to facilitate assessment of the benefits and risks of treatments or to improve our understanding of the impact of a disease or treatment on patients' lives. The incorporation of such data into medical product development and regulation has been increasingly recognized by many stakeholders as vital to ensuring that trans-



Enhancing the experience. New sources of patient data converge with regulatory decision-making—but first, some hurdles in characterizing patient diversity, standardizing data, accessing clinical trials, and effectively disseminating outcomes research to all.

formational new therapies are advanced. Patients are well equipped to identify critical gaps and unmet needs in their own disease areas and then advocate for solutions to meet those needs. Patients can also play a direct role in research through a variety of mechanisms, including helping to set priorities, aiding in the design of clinical trials that measure outcomes that matter, and de-

fining benefits that are clinically meaningful as well as risks that may or may not be acceptable in the treatment of their disease (2). Lastly, patients can provide firsthand information on treatment tolerability, ability to function, and symptom burden.

Several ongoing initiatives have made considerable headway in the collection and use of patient experience data. The Patient-Focused Drug Development Initiative (<http://scim.ag/patient-focus>), the Patient Representative Program (<http://scim.ag/patient-representative>), and the Patient Preferences Initiative (<http://scim.ag/patient-preferences>) are the FDA's efforts to engage patients during the regulatory review processes. The National Cancer Institute (NCI) has developed the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE; <http://healthcaredelivery.cancer.gov/pro-ctcae/>), as part of its commitment to develop quantifiable data about the patient experience.

Despite these efforts, several challenges continue to impede progress in this area. First, patients are not a monolithic group, and thus characterizing patient diversity is difficult. Unique experiences inform attitudes about benefits, risks, and treatment goals. Additionally, perspectives may differ prior to, during, and following treatment and depending on experience with different therapies. Moreover, the experiences of patients who have experienced harm as a result of treatment are rarely shared beyond standard adverse event reporting. Second, the complexity of drug development and regulatory processes may hinder engagement. Although patients want to provide input, they lack familiarity with clinical trials, the policies and process of drug regulation, and awareness of opportunities for engagement. Few mechanisms currently exist for systematic engagement of patients in the drug development continuum.

We therefore propose several ways to better gain patient experience data:

- **Patient training programs.** Improved training and education processes can increase engagement and the robust nature of

Friends of Cancer Research, 1800 M Street, NW, Washington, DC 20036, USA.

*Corresponding author. E-mail: esigal@focr.org

data collected, ensuring increased understanding of multiple disease experiences. Comprehensive training programs for both individuals and organizations need to be developed to facilitate patient involvement in clinical trial design and risk-benefit decisions. Outreach and funding are needed to ensure effective participation. Hosted by think tanks and advocacy groups with deep knowledge of regulatory issues, these programs would feature insights from experts in the field on the drug development and regulatory processes.

• **Generating and publicizing data.** Consistent use of standardized patient-reported outcome tools, such as the PRO-CTCAE, across publicly and privately funded trials would enable standardization and interpretation of the data obtained. For instance, in oncology, development of a core “advanced cancer symptom score”—a method of measuring key symptoms across multiple disease types—should be pursued in order to facilitate standardized data capture and reporting of cancer symptoms (3).

• **Outreach to patients adversely impacted by a treatment.** Capturing data not only from patients who have benefited from a treatment but also from those who did not benefit or who may have been harmed is vital to understanding the impact of a treatment.

• **Publication of negative trial results.** Patient advocacy organizations, researchers, and clinicians should advocate for the publication of negative trial results, to inform our understanding of the full range of patient experiences.

DRUG DEVELOPMENT: OUT IN THE REAL WORLD

A widely cited figure about clinical research in oncology is that only about 3% of adult cancer patients participate in clinical trials. This tiny sample might offer an inaccurate or incomplete picture of a drug’s performance, yet most of what is known about drugs is limited to this information. Ideally, marketing approval would not mark the limit of our understanding of drug performance but instead be the first step in an ongoing process to assess a drug’s impact in real-world populations. “Real world” or “real life” data have been defined by the International Society for Pharmacoeconomics and Outcome Research as “everything that goes beyond what is normally collected in the Phase III clinical trials program” and “a measure in understanding health care

data collected under real life practice circumstances” (4).

Programs such as the FDA’s Sentinel Initiative (<http://scim.ag/sentinel-initiative>), an electronic post-market drug surveillance system, have improved the capture of patient outcomes data in real-world clinical practice, allowing for enhanced safety monitoring of new drugs. However, much information on drug outcomes is not recorded in a way that can inform regulatory decisions or medical practice. With improved data capture from electronic medical records and claims data, many efforts are now under way to address this need, though challenges in data collection and management remain.

First, although off-label drug use is common practice in oncology, particularly for patients who have exhausted all other treatments or for patients with rare cancer types, very little information about off-label use is collected in any systematic way. Second, existing patient experience data collection programs, such as the Sentinel Initiative, the National Medical Device Evaluation System (5), the American Society of Clinical Oncology (ASCO) CancerLinQ (www.institutequality.org/cancerlinq), and the National Patient-Centered Clinical Research Network, PCORnet (www.pcornet.org), will generate an enormous amount of data that needs to be disseminated to inform clinical practice. Data will then need to be organized, interpreted, and incorporated into FDA procedures before they have any impact on patients’ lives. Designing standards and a framework for sharing data while ensuring interoperability pose considerable challenges. Additionally, standards will be needed to integrate data into regulatory and medical practice, including benchmarks for altering labeling and guidelines, which will ultimately inform providers about changes to safety and efficacy data.

Despite these challenges, there are clear steps to facilitate drug development reflecting real-world scenarios. As we learn more from patients receiving treatments outside the clinical trial setting through new and existing programs, these lessons can then be applied to future clinical trial development.

• **Alter clinical trial accessibility.** In an effort to move toward a more realistic representation of the real world within clinical trials, we suggest that outcomes data should be collected from patients who do not meet eligibility criteria for clinical trials; exclusion criteria that lack scientific justification should be minimized to facilitate patient en-

rollment; and broader patient populations should be enrolled while identifying unique patient subsets on which to perform separate efficacy analyses.

• **Rework research infrastructure.** Bringing patient input into research requires a robust infrastructure that encourages institutional collaboration and is designed to yield meaningful results. One reform that can improve trial efficiency is reducing the number of uninterpretable safety reports for products under investigational new drug (IND) applications (6). Similarly, reforms to expand the use of central institutional review boards (IRBs) to minimize trial delays and improve incentives to ensure rapid update of these programs are needed.

• **Use real-world data to bolster existing knowledge.** Existing and future health information technology platforms should enable researchers to conduct randomized trials to maximize the utility of real-world data. In addition, observational data should be used to identify drug effectiveness in small subpopulations of patients with a particular genetic characteristic.

PATIENT VOICES

Drug developers, researchers, physicians, and regulators are forming closer collaborations with patients and their advocates. These collaborations have been critical to identify outcomes and safety signals that are most valuable for informed decision-making prior to drug marketing and during clinical use. The field has made great strides in understanding the appropriate balance of benefits and risks of new drugs. Nevertheless, work is still ongoing to standardize patient experience data collection mechanisms that are needed to inform risk-benefit analysis. Communication of risk-benefit and regulatory uncertainty will be crucial moving forward, where drug labeling will need to be updated to reflect new data, medication guides must be made clear to all patients, and direct-to-consumer advertising must be harnessed for conveying important public health messages.

The path forward involves creating comprehensive patient education programs to improve patient engagement in health care decisions and the research process. Programs must be made available to guide understanding of the drug development and approval process and to educate medical students and practicing physicians. Furthermore, collecting real-world data to enhance understanding of drug performance—and

assimilating data from different sources to allow for maximized use by the greater community—will greatly expand what can be known about drugs in the postmarket setting. Taken together, these steps will incorporate a strong patient voice throughout the process and will improve the quality of care for millions of individuals.

REFERENCES AND NOTES

1. M. Anderson, K. K. McCleary, From passengers to copilots: Patient roles expand. *Sci. Transl. Med.* **7**, 291fs25 (2015).
2. S. Chakradhar, Training on trials: Patients taught the language of drug development. *Nat. Med.* **21**, 209–210 (2015).
3. E. Basch, B. B. Reeve, S. A. Mitchell, S. B. Clauser, L. M. Minasian, A. C. Dueck, T. R. Mendoza, J. Hay, T. M. Atkinson, A. P. Abernethy, D. W. Bruner, C. S. Cleeland, J. A. Sloan, R. Chilukuri, P. Baumgartner, A. Denicoff, D. St Germain, A. M. O'Mara, A. Chen, J. Kelaghan, A. V. Bennett, L. Sit, L. Rogak, A. Barz, D. B. Paul, D. Schrag, Development of the National

Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *J. Natl. Cancer Inst.* **106**, dju244 (2014).

4. L. Annemans, M. Aristides, M. Kubin, Real-Life Data: A Growing Need. *ISPOR Connections*, **13**(5): 8-12 (2007); www.ispor.org/News/articles/Oct07/RLD.asp.
5. Medical Device Registry Task Force & the Medical Devices Epidemiology Network, Recommendations for a National Medical Device Evaluation System: Strategically Coordinated Registry Networks to Bridge Clinical Care and Research, 20 August 2015; www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhreports/ucm459368.pdf.
6. U.S. Department of Health and Human Services, FDA, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, December 2012; <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf>.

Acknowledgments: We thank the panel members who contributed to these recommendations: J. Abrams (NCI); J. S. Akman (George Washington University); M. Anderson

(FasterCures); J. W. Beetsch (Celgene); C. Bens (Alliance for Aging Research); R. Califf (FDA); R. Canetta (Bristol-Myers Squibb); A. Coukell (Pew Charitable Trusts); G. Dahlman (National Patient Advocate Foundation); A. Ferris (LUNGevity Foundation); M. Fleury (American Cancer Society Cancer Action Network); K. Holcombe (BIO); N. Hunter (FDA); K. Jones (Genentech); P. Kluetz (FDA); J. Leff (Deerfield Management); T. Mullin (FDA); R. Pazdur (FDA); A. Pope (Institute of Medicine); A. Ray (Janssen Pharmaceuticals); N. Roach (Fight Colorectal Cancer); D. Roth (FDA); R. Schilsky (ASCO); R. Schneider (Pfizer); J. Selby (Patient-Centered Outcomes Research Institute); R. Sherman (Greenleaf Health); J. Shuren (FDA); and P. Tenaerts (Clinical Trials Transformation Initiative). **Funding:** The FOCR forum and corresponding full report were supported by a grant from the Burroughs Wellcome Fund. **Data and Materials Availability:** The full forum white paper is available at <http://www.focr.org/patient-experience-whitepaper>.

10.1126/scitranslmed.aad5233

Citation: R. Hohman, M. Shea, M. Kozak, S. Roberts, J. Allen, E. Sigal, Regulatory decision-making meets the real world. *Sci. Transl. Med.* **7**, 313fs46 (2015).

Science Translational Medicine

Regulatory decision-making meets the real world

Ryan Hohman, Michael Shea, Marina Kozak, Samantha Roberts, Jeff Allen and Ellen Sigal

Sci Transl Med 7, 313fs46313fs46.
DOI: 10.1126/scitranslmed.aad5233

ARTICLE TOOLS

<http://stm.sciencemag.org/content/7/313/313fs46>

RELATED CONTENT

<http://stm.sciencemag.org/content/scitransmed/7/291/291fs25.full>
<http://stm.sciencemag.org/content/scitransmed/7/298/298ps16.full>
<http://stm.sciencemag.org/content/scitransmed/2/37/37cm18.full>
<http://stm.sciencemag.org/content/scitransmed/4/131/131ra49.full>
<http://stm.sciencemag.org/content/scitransmed/7/297/297ed10.full>
<http://stm.sciencemag.org/content/scitransmed/6/221/221fs5.full>
<http://stm.sciencemag.org/content/scitransmed/5/182/182fs13.full>
<http://stm.sciencemag.org/content/scitransmed/7/284/284fs15.full>
<http://stm.sciencemag.org/content/scitransmed/5/168/168ed1.full>
<http://stm.sciencemag.org/content/scitransmed/4/152/152ps16.full>
<http://stm.sciencemag.org/content/scitransmed/7/315/315ps22.full>
<http://science.sciencemag.org/content/sci/351/6271/325.full>
<http://stm.sciencemag.org/content/scitransmed/8/347/347ed10.full>

REFERENCES

This article cites 3 articles, 1 of which you can access for free
<http://stm.sciencemag.org/content/7/313/313fs46#BIBL>

PERMISSIONS

<http://www.sciencemag.org/help/reprints-and-permissions>

Use of this article is subject to the [Terms of Service](#)

Science Translational Medicine (ISSN 1946-6242) is published by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005. The title *Science Translational Medicine* is a registered trademark of AAAS.

Copyright © 2015, American Association for the Advancement of Science