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COMMENTARY

Inaugural Conference on Incorporating Patient-Reported Outcomes and Patient Preference Information into Clinical Research, Clinical Care, and Risk-Benefit Assessments for Neurodegenerative Diseases

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The Georgetown University Patient Reported Outcomes for Neurodegenerative Diseases Symposium, held on 27–28 April 2016 in Washington, DC, USA, brought together a diverse group of patients and their families, academia, government [US Food and Drug Administration (FDA), National Institutes of Health (NIH)], and industry to discuss patient-reported outcomes (PROs) and patient preference information (PPI) measures in research, clinical practice, and regulatory decision-making. Many stakeholders and their organizations have advocated for the inclusion of patients' perspectives in clinical care, research, and regulatory decisions. The consensus is that PROs and patient preferences are important and necessary to inform the decisions that are made by healthcare providers, patients, and their families, as well as the information collected by researchers and medical product manufacturers and reviewed by regulators in the development of medical products [1, 2].

All participants had a stake in the development of safe and effective treatments for Alzheimer, Huntington, and Parkinson diseases. The symposium objectives were to both build new and strengthen existing relationships between patients, family caregivers, researchers, clinicians, pharmaceutical and medical device manufacturers, and regulatory decision-makers, and also to provide a forum in which participants could convene, collaborate, and critically assess areas of unmet need. The symposium included keynote addresses and workshops focused on three topics: (1) "PROs for Clinical Research and Medical Product Development"; (2) "PROs for Clinical Care"; and (3) "Patient Preferences for Risk-Benefit Assessments".

Karen Anderson, MD (Georgetown University), provided an introduction to the meeting and outlined the mission of the working groups. Plenary sessions were held to provide an overview of topic areas and to flag particular unmet needs. These included "PROs for Clinical Trials and

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Medical Product Development" by Joohee Sul, MD, Medical Officer, Center for Drug Evaluation and Research, FDA; "PROs for Clinical Care" by Lori Frank, PhD, Associate Director, Patient-Centered Outcomes Research Institute (PCORI); and "Patient Preferences for Risk-Benefit Assessments for Regulatory Decision-Making" by Kathryn O'Callaghan, Associate Director for Science and Strategic Partnerships (Acting), Center for Devices and Radiological Health, FDA.

The "PROs for Clinical Research and Medical Product Development" session, co-chaired by Ray Dorsey, MD, MBA (University of Rochester School of Medicine), Fernando Pagan, MD (Georgetown University), and patient John Creveling examined the utility and challenges of incorporating PROs as outcomes in clinical trials for neurodegenerative diseases. The group identified a need for different PRO measures for different stages of each disease and caregiver input captured in additional caregiver-specific measures. Challenges identified included adequate time to develop and pilot scales, sampling bias potentially present in a research population, and access to and availability of electronic devices for patients to report symptoms remotely. Because statistical power calculations traditionally rely on quantitative outcomes, the workgroup agreed that in cases of qualitative PROs, novel analysis methods are needed that are reliable, valid, and clinically meaningful. The discussion generated suggestions for next steps:

1. Use existing scales that are validated for specific disease states, work to improve these scales for reproducibility in clinical research, and simultaneously explore novel PRO measures in future trials.
2. Engage multiple stakeholders groups (including patients, caregivers, industry, clinicians, researchers, and regulatory) in the development of new PROs or the refinement of existing ones.
3. Identify new funding sources for development and validation of PROs.
4. Utilize advantages of technology (including electronic health records) to capture real-world data with greater frequency and objectivity, while cognizant that devices may pose additional challenges for neurodegenerative disease patients.

The "PROs for Clinical Care" session, co-chaired by Tanya Simuni, MD (Northwestern University), MaryAnne Sterling, a caregiver, and Pierre Tariot, MD (Banner Health), examined the utility and challenges in using PROs to inform patient care by aligning patient, caregiver, and clinician goals and expectations. Within this broad topic, the group identified four categories of unmet needs: communication, access to care, education, and patient/provider partnership. Obstacles to addressing these needs included lack of time, need for privacy and security, and limited financial and geographic access to team care. The discussion generated suggestions for next steps:

1. Implement two-structured communication guidelines: first, a 'code of ethics for communication' to address how patients communicate differently than clinicians about their disease; and, second, guidelines and tools that assist patients and care partners to effectively communicate their needs and to feasibly coordinate self-advocacy and care.
2. Develop structured tools to teach patients clinical appointment preparation (what and how the doctor wants to know about the patient's conditions and concerns), train clinicians to better listen to patients/caregivers and ask questions (considering ethnic, social, cultural, and gender impacts of these disorders), and incorporate patient-reported measures into clinical care.
3. Improve the existing model of patient/provider partnership to better incorporate caregiver input and perspective into the patient/provider partnership and clearly articulate all parties' expectations.
4. Restructure current neurodegenerative disease clinical care funding to mirror the clinical trial model, allowing for longer visits, a multidisciplinary team, facilitated appointments, and follow-up provided by a care coordinator.

The "Patient Preferences Information (PPI) for Risk-Benefit Assessments" session, co-chaired by Telba Irony, PhD (Center for Biologics Evaluation and Research, FDA), Tara LoCastro, MBA, caregiver, and Bernard Ravina, MD (Voyager Therapeutics), examined the application of PPI in assessing the benefits and risks of experimental interventions. The workshop group highlighted prior work that identified the unmet needs for effectively incorporating patient preferences in all stages of research, increased research to characterize patient and caregiver preferences, and effective methods to capture this information. Many barriers to designing patient preference studies became evident from the discussion, including clinicians' or researchers' differing assumptions about patient preferences. One example is the assumption that risk-benefit assessments change over time due to disease progression, increase in cognitive and behavioral impairment, or new information. However, such data have not been systematically collected. Additional barriers to reliability and the longitudinal assessment of risk-benefit patient preference data include product changes, treatment purpose (targeting symptoms vs. disease altering), and the role of emotion and insight in decision-making. Cognitive decline exacerbates challenges to effectively capturing patient preferences, and methods may need to further examine these issues in patients with neurodegenerative disorders. Lastly, smaller

companies are at a disadvantage to effectively include patient preferences in clinical research due to their need to limit study development costs, especially in early stages of development. The discussion generated suggestions for next steps:

1. Shift focus from what is wrong with the patient to the patient's priorities by directly asking the patient to judge his or her own healthcare needs.
2. Fund research to incorporate patient perspectives at multiple timepoints during the development lifecycle, including earlier, throughout, and at the end. This will clarify how patient preferences change with disease progression.
3. Require collecting risk-benefit PPI in post-market surveillance if there is uncertainty or the patient population is expected to differ appreciably from the research population. Post-marketing insight is often a missed opportunity to access patient and family member insights and lessons learned.

Working groups presented these summaries at the end of the symposium. Commentary was then provided by Joel Grace, a Parkinson disease patient and advocate, who gave the "Patient Perspective Closing Remarks". Ira Shoulson, MD (Georgetown University), summarized the discussion and findings.

The symposium demonstrated the need to increase patient engagement for development of PROs and PPIs in the settings of clinical care, research, and risk-benefit assessments for neurodegenerative diseases. All stakeholders had a vested interest in enhanced patient engagement. The *regulators*, who make decisions about medical products, benefit from patient information to decide in the best interest of patients. *Researchers in academia and innovators in industry*, who work together to create and develop treatments, rely on patients and families to volunteer for clinical trials to test investigative treatments and use these treatments once they are FDA approved for marketing. Accordingly, researchers and innovators need to understand and value patient reports and their preferences. *Patients and care partners* rely on drug developers and clinicians, who create and prescribe treatments. Therefore, patients and care partners stand as eager collaborators to develop better care and treatment.

The symposium highlighted the dearth of existing research in this area, and identified a number of tangible next steps for stakeholders to improve communication between all stakeholders on related issues. While a scarcity of resources presents a challenge, many next steps were suggested to advance PROs and patient preferences in clinical research and medical product development, PROs for clinical care, and PPI for risk-benefit assessments for regulatory decision-making. Future patient-centered symposia and workshops are expected to advance progress for those affected by neurodegenerative diseases.

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Compliance with Ethical Standards

Conflicts of interest Karen E. Anderson, MD, is a consultant for Teva Pharmaceutical Industries and previously a consultant for Auspex Pharmaceuticals. She received payments for clinical trials as a site investigator and as overall study principal investigator (PI) and co-PI from Teva and from Auspex. She receives salary support from the Griffin Foundation. She received travel support to attend the symposium. E. Ray Dorsey, MD, has received compensation for consulting activities from Teva. He accepted travel support for the symposium and an honorarium as a working group co-chair. Telba Irony, PhD, has no conflicts or financial disclosures to report. Fernando Pagan, MD, is employed by Medstar Georgetown University Hospital and has received consulting support from Teva Pharmaceuticals and accepted travel support for the symposium and an honorarium as working group co-chair. He has received research grants from Teva Neuroscience, US WorldMeds, and Medtronic Education Grant; and received payment for lectures from Teva, Impax, Acadia, US WorldMeds, Lundbeck, and Medtronic. Jennifer L. Purks, BS, is employed by Georgetown University and has received salary support from Auspex Pharmaceuticals and Teva Pharmaceutical Industries as a site clinical trial coordinator. She was given travel support and an honorarium to attend and present two research posters at the symposium. Bernard Ravina, MD, accepted travel support for the symposium and an honorarium as a working group co-chair. He is an employee and equity holder in Voyager Therapeutics. Tanya Simuni, MD, has received consulting support and served as a speaker and accepted an honorarium from Teva Pharmaceuticals. Dr. Simuni accepted travel support for the symposium and an honorarium as a working group co-chair. Ira Shoulson, MD, was a paid consultant (2014–2015) to Auspex Pharmaceuticals, one of the sponsors of the symposium. He was not paid an honorarium or any fees for his participation in the symposium. He receives salary support from Georgetown University via the US Food and Drug Administration–Georgetown University Center of Excellence in Regulatory Science and Innovation (CERSI; FD004319). Pierre Tariot, MD, has received consulting fees from Auspex Pharmaceuticals and accepted travel support for the symposium and an honorarium as a working group co-chair. Erin E. Wilhelm, MPH, receives salary support from Georgetown University and the US Food and Drug Administration-Georgetown University Center of Excellence in Regulatory Science and Innovation (CERSI; FD004319); she was given travel support to attend the symposium. John Creveling, Tara M. LoCastro, and MaryAnne Sterling accepted travel support for the symposium and honoraria as working group co-chairs.

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