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Neuroprosthetics and the science of patient input

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Abstract

Safe and effective neuroprosthetic systems are of great interest to both DARPA and CDRH, due to their innovative nature and their potential to aid severely disabled populations. By expanding what is possible in human-device interaction, these devices introduce new potential benefits and risks. Therefore patient input, which is increasingly important in weighing benefits and risks, is particularly relevant for this class of devices. FDA has been a significant contributor to an ongoing stakeholder conversation about the inclusion of the patient voice, working collaboratively to create a new framework for a patient-centered approach to medical device development. This framework is evolving through open dialogue with researcher and patient communities, investment in the science of patient input, and policymaking that is responsive to patient-centered data throughout the total product life cycle. In this commentary, we will discuss recent developments in patient-centered benefit-risk assessment and their relevance to the development of neural prosthetic systems.

1. Introduction

Efforts by the Defense Advanced Research Projects Agency (DARPA) to stimulate the creation of technology to restore and enhance the capabilities of amputees following limb loss have been characteristically ambitious. Over the past ten years, DARPA programs such as Revolutionizing Prosthetics (RP), Reliable Neural-Interface Technology (RE-NET), and Hand Proprioception and Touch Interfaces (HAPTIX) have made major contributions to the area of regenerative medicine known as neuroprosthetics, funding efforts to develop novel robotics and brain and nerve interface technologies that could enable the restoration of complete, natural functionality. DARPA's interest in these types of device systems derives not only from their specific capabilities, but also from the general class of biomedical challenge that they represent: how to safely and effectively interface between biological and technological systems. This challenge is as difficult as it is important.

Progress in neuroprosthetics is also aligned with the vision of FDA's Center for Devices and Radiological Health (CDRH), which is that patients in the U.S. have access to high quality,

safe, and effective medical devices of public health importance first in the world (“CDRH Mission, Vision and Shared Values,” 2015). Brain- and nerve-interfacing prosthetics have a high degree of public health importance (Maisel, 2014), both because of the technological progress they could represent, and because of the patient population they could serve, which includes thousands of severely disabled individuals, among them many Service members and veterans. Recognizing this public health importance, CDRH has recently taken steps to obtain feedback on scientific and clinical considerations associated with these prosthetics, for example, hosting a public workshop in 2014 on “Brain-Computer Interface Devices for Patients with Paralysis and Amputation” (FDA, 2014; Bowsher et al., 2016).

Bringing novel safe and effective devices to patients means determining that a device’s potential benefits outweigh its potential risks 21 CFR 860.7(d)(1), and that it will provide clinically significant results (21 CFR 860.7 (e)(1)). While the probability of a particular beneficial or adverse event can be estimated by CDRH scientists, clinicians, and engineers based on data provided by sponsors or available in the published literature, patient input improves the estimate of the *weight* or *importance* of an event. Since this estimation of weight is a key part of benefit-risk assessment, it follows that patient input is as well. In light of this, and with awareness of the increasing amount and quality of information available to patients, CDRH has recently become more involved in developing the science of assessing patient views so that the resulting data can inform regulatory decisions. The purpose of this commentary is to survey recent highlights of this involvement and to describe their relevance for neuroprosthetics.

2. Patient-centered risk-benefit assessment in regulatory practice

For many years, CDRH has included a patient representative on advisory panels, which are used to obtain independent expert advice about issues related to the safety and effectiveness of medical devices (CDRH and CBER, 2016). While input from these representatives is valuable, it can be difficult to draw generally applicable conclusions from such input, since individual perspectives cannot account for the heterogeneity of patient experiences. Individual perspectives also do not permit quantification of the importance assigned to specific device benefits and risks. Accordingly, over the past six years (Fig. 1), FDA has engaged with the medical device community, including patients, researchers, and developers, to collaborate on a framework with the potential to increase both the quality and the quantity of available data on patient perspectives, in order to produce more actionable conclusions. This engagement has taken various forms, including guidance documents, public workshops, the formation of an advisory committee, commentaries, and peer-reviewed research.

In 2012, FDA published the guidance document “Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications” (CDRH and CBER, 2012). Among the factors suggested for consideration during benefit-risk assessment of a device, this guidance includes patient tolerance for risk and perspective on benefit. It explains that FDA recognizes heterogeneity in risk tolerance among patients, and that this variability may be correlated with factors such as severity of the disease or condition, disease chronicity, and the availability of alternative treatment options. The document further highlights the utility of validated quality of life measures for

understanding and communicating with patients about the potential impact of a device. Finally, the guidance includes a section of hypothetical examples to demonstrate how various factors might impact benefit- risk determinations. In the first hypothetical example, a sponsor provides data to FDA showing that patients would accept the probability of benefit given the risks accompanying device implantation, and these data contribute to the premarket evaluation outcome. The 2012 guidance set the stage for the development of a comprehensive framework for collecting, including, and analyzing patient preference data.

Following the 2012 guidance, in 2013 FDA hosted a public workshop entitled “The Patient Preference Initiative: Incorporating Patient Preference into the Medical Device Regulatory Process” (FDA, 2013). This workshop provided patients, researchers, device developers, and regulators with a venue to discuss strategies for the incorporation of patient perspectives on benefits and risks into FDA's development of regulatory policy. There was an emphasis on advancing the science of quantifying these perspectives, with the first day's topics focused on data collection methods, tools, and validation. This workshop laid the foundation for a draft guidance published in 2015, outlining a more complete framework for the use of patient preference information in premarket submissions. Public comments on the draft guidance were accepted from 18 May 2015 through 18 August 2015 and the final guidance, entitled “Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling,” has just been published (CDRH and CBER, 2016).

This document primarily addresses considerations relevant to device approval, including the use of qualitative and quantitative patient preference information, how premarket reviewers might consider patient preference information, qualities of patient preference studies that increase relevance to benefit-risk assessment, and how patient preference information might be communicated to clinicians and consumers. An appendix includes an overview of several quantitative approaches that could be used to collect patient preference information.

A separate draft guidance document published in June 2015, “Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions (IDEs)” (CDRH and CBER, 2015), discusses the use of patient preference information when assessing the benefits and risks of investigational devices. This draft guidance considers the possibility that an IDE application may be approved even if only a subset of patients would accept the benefit-risk tradeoffs, as long as study participants are able to give adequately informed consent. Devices intended to yield improvements in health-related quality of life, as is the case for many neuroprosthetics, are specifically listed as a one type for which patient preference information might be particularly informative. This guidance's draft status indicates that FDA has not yet made a decision on the extent to which the proposals will be adopted (see Sidebar). Together with previous guidance documents and workshops, these recent documents set the stage for patient-centered research and regulatory decision-making for medical devices.

FDA has solicited patient and industry input into defining the role of patient engagement in the regulatory process in several ways, including inviting comments in response to draft

guidances and establishing a Patient Engagement Advisory Committee (PEAC). The PEAC is the first FDA advisory committee focused wholly on patients. It will be comprised of patients, patient advocacy groups, and experts, who will advise the FDA Commissioner on patient-related issues as they continue to evolve (Hunter and Califf, 2015). The establishment of the PEAC ensures that the ongoing conversation about patient-centered medical device development and regulation will continue.

3. The science of patient preference

CDRH is contributing to the science of assessing patient preferences via both internal regulatory science projects and joint efforts with other members of the Medical Device Innovation Consortium (MDIC), a non-profit public-private partnership whose members include the FDA, National Institutes of Health, Centers for Medicare & Medicaid Services, and dozens of patient groups, medical device companies, and non-profit organizations. MDIC has created a framework for assessing and using patient preferences in device development and regulation, and compiled a catalog of quantitative methods for collecting patient preference information to ensure devices meet patient needs (MDIC, 2015). While quality-adjusted life years (Vergel and Sculpher, 2008) and quality of life (Guyatt et al., 1993) are traditional patient-centric measures of device outcomes, they are broad concepts that are best suited to use in large-scale clinical trials. In contrast, the qualitative and quantitative approaches in the MDIC framework are suitable to a broader range of stages in the medical device development life cycle. In the regulatory arena, these quantitative approaches, which leverage the experiences and opinions of patient populations, are a significant step forward from previous practice, in which the patient perspective was provided by a single representative or patient group. Quantitative approaches permit the description of heterogeneous patient views, and the identification of needs or preferences that may only be associated with a subset of patients. Dissemination of these methods equips both patient advocacy groups and device manufacturers with the tools to obtain scientific data about patient preferences that can be considered in premarket review and incorporated into the total product life cycle.

Although the field of quantitative patient preference assessment is relatively young, it builds on a long history of insight from the social sciences and behavioral economics (McFadden, 1976; Green et al., 2001). More recently, several studies with medical applications have appeared in the literature (for a review, see Hauber et al., 2013). One example of a patient group-led approach involved Parent Project Muscular Dystrophy (PPMD, Peay et al., 2014). PPMD collaborated with researchers at the Johns Hopkins Bloomberg School of Public Health to survey over 100 caregivers of Duchenne muscular dystrophy patients using best-worst scaling, an approach in which survey participants select the best and worst features of potential therapies (McIntosh and Louviere, 2002). Once they had determined the importance of potential treatment benefits and risks to these caregivers, they learned that caregivers would accept serious risks, such as increased risk of sudden death or increased risk of lifelong disability, if a treatment stopped or slowed the progression of weakness. In this case, patients were not surveyed directly; however, the framework is directly applicable to doing so.

In another recent study, researchers from CDRH and RTI Health Solutions collected data from obese patients on preferences for potential weight loss device benefits and risks using a discrete-choice survey (Ho et al., 2015). They created a tool that could be used to estimate minimum weight loss required or maximum acceptable mortality risk based on several device attributes, and in 2015 this evidence factored into the approval of the first obesity device since 2007 (O'Callaghan and Shuren, 2015). This initial case of the use of patient preference data in a benefit-risk determination has paved the way for the submission of additional patient preference studies to CDRH.

4. Patient-centered neuroprosthetic development

How will ongoing progress in assessing and integrating patient input affect the development of neuroprosthetics? Present and future neuroprosthetic systems may incorporate advanced robotic limbs; implantable interfaces to muscle, nerve, and brain; and stimulation to provide sensory feedback. It will be important to understand patients' perspectives on the resulting benefits and risk changes in order to design devices that are relevant to patient needs, run clinical trials that accurately assess the devices' performance, and take well-informed premarket and postmarket regulatory actions. Individuals with amputations are well-qualified to identify their own needs and express opinions on novel benefits and risks, based on their own experiences before injury and while adapting to amputation and existing prosthetic technology.

Patient preference data may be particularly important for prosthetic devices, in which there is a potential relationship between patient preference and device performance that does not exist for most medical devices. Increased early device acceptance may lead to increased usage (Biddiss and Chau, 2008) and, subsequently, increased functional performance with the device (Davidson, 2002), creating a positive feedback loop. A corollary negative feedback loop may exist for devices that fail to meet prosthesis users' initial expectations, and are subsequently rejected. Approximately one quarter of upper limb prostheses are rejected (Biddiss and Chau, 2007a); a survey to determine the causes has identified factors such as low prosthesis functionality, discomfort, difficulty using the device, heaviness, and lack of sensory feedback from the device (Biddiss and Chau, 2007b). Prosthesis users report a variety of activities that are challenging with their prostheses, including household activities, sports and hobbies, and activities of daily living. They list comfort and function as the highest design priorities, with a focus on socket-related features such as heat and weight and improved functional control such as grasp, wrist control, and dexterous movements (Biddiss et al., 2007).

These surveys have provided initial guidance to prosthetic researchers and device designers, but as advances in neuroprosthetics have created radically new technical capabilities, additional insight is needed into user needs and preferences as they relate to advanced robotic limbs with many more degrees of control, sensory feedback, and implantable device components. Recently, a survey determined that over 60% of individuals with upper limb loss were interested in trying novel prosthesis control techniques that require peripheral surgery (Engdahl et al., 2015). Information on which benefits these individuals would

require, and with what likelihood, in order to accept the additional risks would help to target device development and inform device assessment.

Up to this point we have confined our discussion to the assessment of patient views on the weight or importance of particular device attributes or outcomes. Another important element of patient input is the use of Patient-Reported Outcomes (PROs). In contrast to patient preferences about benefits and risks, PROs are not assessments of the importance of a device feature; rather, they are similar to other clinical trial endpoints in that they are assessments of a treatment benefit. PROs differ from other types of endpoints in that they are provided directly by the patient, without interpretation by a clinician or anyone else. Typically taking the form of questionnaires, they have been used as primary or key secondary clinical trial endpoints for a wide variety of indications (Varma et al., 2010; Deisseroth et al., 2012). The 2009 guidance document “Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” (CDER, CBER, and CDRH, 2009), explains how FDA reviews and evaluates patient-reported outcome (PRO) instruments used to support claims in approved medical product labeling.

A number of PRO instruments exist for upper limb amputation and prosthesis use. They are useful for many reasons: because it is difficult to observe individualized activities of daily living in an artificial setting; because quality of life, which is primarily assessed as a PRO, is a major anticipated outcome of improved function with prosthesis use; and because prosthesis users are well-qualified to report on device performance. For example, two widely-used clinical self-report measures were used in clinical trials of the DEKA Arm (Resnik et al., 2014b). The two PRO instruments used to assess the impact of the prosthesis on user functionality were the Upper-Extremity Functional Scale (UEFS, Burger et al., 2008; Heinemann et al., 2003), and the Patient-Specific Functional Scale (PSFS, Stratford et al., 1995). With the UEFS, prosthesis users score their abilities on a difficulty scale for a variety of unilateral and bilateral activities. The PSFS allows users to identify specific important activities that are difficult for them, and to provide follow-up assessments on those activities over time. For PRO instruments such as these, the 2009 guidance document identifies several factors to consider during evaluation, including the population enrolled in the clinical trial, the clinical trial objectives and design, the instrument's conceptual framework, and the instrument's measurement properties.

Neuroprosthetic outcomes, such as functional performance, activities, and participation, can be highly patient-specific, and it may be most appropriate to permit prosthesis users to select personally important tasks for evaluation. Both the PSFS and the Assessment of Capacity for Myoelectric Control (ACMC, Hermansson et al., 2005) are examples of patient-specified prosthesis outcome measures. A potential precedent is developing for this approach in the area of drugs, in which a recent draft guidance “Migraine: Developing Drugs for Acute Treatment” (CDER, 2014) suggests that patients might prospectively identify a bothersome symptom as a co-primary endpoint in a migraine drug clinical trial.

In 2014, FDA allowed marketing in the United States of the DEKA Arm System, development of which was funded by the DARPA Revolutionizing Prosthetics (RP) program. Clinical trials of the DEKA Arm described in the literature made extensive use of

patient input, including patient-informed design (Resnik et al., 2014b), PROs, patient-specified endpoints (Resnik et al., 2014a), and patient preference information (Resnik et al., 2013). Patient-informed design was achieved by involving Veterans Administration researchers, who gathered feedback from DEKA Arm users during clinical trials to contribute to a continual prototyping process (Resnik et al., 2014b). Patient-reported outcome measures used were the UEFS and the PSFS, and were administered twice with subjects' existing prostheses and several times as subjects were trained to use the DEKA Arm over a number of visits. Resnik et al. also collected qualitative patient preference information about the desirability of the prosthesis, user-perceived benefits of the prosthesis, and concerns about taking the prosthesis home.

Future neuroprosthetics will benefit from leveraging elements of the DEKA Arm's approach as well as additional opportunities to incorporate patient needs and preferences into the product lifecycle (Fig. 2). Initial data to inform design ideation and prototyping may often be qualitative. For example, socket design, cosmesis, (Biddiss and Chau, 2007a), and pain (Østlie et al., 2011) have been identified as areas that are under-served by ongoing research. Subsequently, quantitative methods such as stated preference surveys (Hauber et al., 2013; Peay et al., 2014; Ho et al., 2015; MDIC, 2015) can identify population-level needs and reactions to the most likely risks for potential device designs. Given the heterogeneity of prosthesis users' needs and approaches to prosthesis use (Østlie et al., 2012), clinical trials are more likely to accurately represent patient experiences if they incorporate patient-specified endpoints and patient-reported outcomes on functional abilities and resulting quality of life. Several measures have been used in the literature to assess prosthesis user quality of life. The Trinity Amputation and Prosthesis Experience Scales (TAPES) was developed specifically for adults with upper or lower limb amputations and includes sections on psychosocial adjustment, activity restriction, and satisfaction (Gallagher and MacLachlan, 2004). Prosthetic clinics and research groups have also used validated quality of life surveys that are not specific to amputation, such as the Nottingham Health Profile (NHP, Hunt et al., 1985) and the Short Form 36 Health Survey (SF-36, Ware, 2008).

Clinical trials are also an excellent opportunity to collect revealed-preference data (MDIC, 2015) for device benefits and risks that are informed by experience, rather than hypothetical preferences. Any relevant patient preference studies and clinical trials may be included in an FDA submission, giving regulators additional information to inform the benefit-risk assessment, which may be particularly relevant due to the highly novel nature of many neuroprosthetics under development. The use of patient-reported outcomes, patient-selected clinical trial endpoints, and patient preference information in device development and assessment promises to lead to the creation of neuroprosthetics that are more targeted to patient needs and preferences, data that are relevant to the regulatory process, and restored functionality for wounded Service members and veterans.

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Abbreviations

ACMC	Assessment of Capacity for Myoelectric Control
BCI	Brain-Computer Interface
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
DARPA	Defense Advanced Research Projects Agency
EMG	electromyogram
HDE	Humanitarian Device Exemption
IDE	Investigational Device Exemption
MDIC	Medical Device Innovation Consortium
NHP	Nottingham Health Profile
PMA	Premarket Approval
PRO	patient-reported outcome
PSFS	Patient-Specific Functional Scale
SF-36	Short Form 36 Health Survey
TAPES	Trinity Amputation and Prosthesis Experience Scales
UEFS	Upper-Extremity Functional Scale

SIDEBAR: Guidance and Draft Guidance Documents

- **Guidance documents** are statements published by FDA that represent current Agency thinking on a topic. Guidance documents do not establish legally enforceable rights or responsibilities. They do not legally bind the public or FDA; however, because they represent the agency's current thinking, FDA employees may depart from guidance documents only with appropriate justification and supervisory concurrence (21 CFR 10.115).
- **Draft guidances** are proposals which may be adopted in whole, in part, or not at all. They are published to the internet with accompanying notification in the Federal Register (federalregister.gov). and public comments are collected for a period which usually spans 30-180 days, but can be longer or shorter with appropriate justification. Specific instructions for providing input to the FDA are provided in each draft guidance.

Fig. 1.
Timeline of recent FDA activity related to patient-centered benefit/risk assessment.

Fig. 2.

A patient-centered total product lifecycle. Patient preferences and patient-owned data are incorporated into the process of technology discovery and device ideation. Patient-sensitive design controls and patient-inspired innovation feed into device invention and prototyping. Patient-sparing test methods, such as the use of modeling and simulation, speed the pre-clinical testing process and make it safer for patients. Clinical trials are conducted with patient-assembled cohorts, using patient-informed clinical trial design, patient-reported outcomes, and patient-selected endpoints. The benefit-risk determination during premarket review is informed by patient preferences. Labeling communicates device information to patients appropriately. Once the product is on the market, patients are involved in shared clinical decision making. Post-market monitoring includes patient-reported outcomes, and communication about post-market monitoring is patient-directed. (CDRH and CBER, 2016).