

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Rehabilitation Research 2020: Envisioning a Functional Future

Thursday, October 15

Introduction and Welcome

*Diana Bianchi, M.D., Director,
Eunice Kennedy Shriver National
Institute of Child Health and
Human Development (NICHD)*

Dr. Bianchi welcomed participants to the conference (via a prerecorded message—one of several novel approaches taken to facilitate the virtual meeting). She thanked the cosponsors that joined NICHD in coordinating the event: the National Institute of Neurological Disorders and Stroke (NINDS), the National Center for Complementary and Integrative Health, the National Institute on Aging, and the National Institute on Deafness and Other Communication Disorders. Dr. Bianchi welcomed the new director of NICHD's National Center for Medical Rehabilitation Research (NCMRR), Theresa Cruz, Ph.D.

Dr. Bianchi pointed out that 2020 has been a particularly challenging year. The COVID-19 pandemic has made it difficult

VIRTUAL EXHIBIT HALL

Eunice Kennedy Shriver National Institute of Child Health and Human Development

- National Center for Medical Rehabilitation Research
- Medical Rehabilitation Research Resource Network

Federal Partners

- National Science Foundation
- National Institute on Disability, Independent Living, and Rehabilitation Research (part of the Administration for Community Living of the U.S. Department of Health and Human Services)
- U.S. Department of Veterans Affairs

Trans-NIH Programs

- Brain Research through Advancing Innovative Neurotechnologies® Initiative
- Helping to End Addiction Long-termSM Initiative
- Stimulating Peripheral Activity to Relieve Conditions program
- *All of Us* Research Program
- NICHD Data and Specimen Hub
- NIH Common Data Element Repository and National Institute of Neurological Disorders and Stroke common data element recommendations
- NIH Common Fund
- NIH Molecular Transducers of Physical Activity in Humans Consortium
- NIH Office of Data Science Strategy
- National Library of Medicine data sharing repository

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

for many people to access rehabilitation services. The related economic strain has taken a toll on people with physical disabilities and their families. The issue of systemic racism has come to the forefront, compelling decision-makers to acknowledge the need to study disparities as they develop the research agenda. Dr. Bianchi noted that the draft research themes and objectives for the 2021 National Institutes of Health (NIH) Research Plan on Rehabilitation Research specifically address health disparities research (under Theme A, Rehabilitation Across the Lifespan) and training a diverse workforce (under Theme F, Building Research Capacity and Infrastructure).

Conference participants were invited to visit the virtual exhibit hall to learn more about resources, services, and opportunities provided by various federal entities (see the box, Virtual Exhibit Hall). Dr. Bianchi encouraged participants to browse the nearly 100 posters provided, organized according to the draft themes of the Research Plan. Throughout the conference, participants took part in moderated discussions in the online Networking Lounge on the six draft themes. (See the appendix for highlights from the Networking Lounge discussions.) Speakers' presentations and all the information provided in the Exhibit Hall and the poster session will be archived for later viewing.

Keynote

Jenny Lay-Flurrie, M.B.A., Chief Accessibility Officer, Microsoft

Moderator: Alison Cernich, Ph.D., Deputy Director, NICHHD

Disability can affect anyone at any time, Ms. Lay-Flurrie pointed out, whether it is permanent, temporary, or situational. People with disabilities have an unemployment rate twice as high as those without, yet they represent a significant pool of potential workplace talent. Some businesses, such as Microsoft, have embraced the talent pool and have seen higher revenues, higher net incomes, and better performance as a result. Disability can be a strength if the company has the right environment to attract and empower people with disabilities.

The COVID-19 pandemic has highlighted some of the challenges people with disabilities face and exemplified the need for inclusive design. For example, many more people are now working from home—something people with disabilities have been striving to normalize for years. Demand for Microsoft tools such as closed captioning and reading support apps has increased dramatically since March 2020. Accessibility has never been more important.

Microsoft began focusing on access for people with disabilities in the 1990s. Ms. Lay-Flurrie joined the company in 1995 and did not disclose her profound deafness to her coworkers until she found herself struggling. She shared her challenges and joined with other employees with disabilities to create an accessible community at Microsoft. Ms. Lay-Flurrie said the community

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

provides her a wealth of understanding and empowerment that ultimately benefits the company.

The Microsoft Accessibility Leadership Team developed a model to assess what accessibility should look like, going beyond products to understand the research, hiring practices, and environment that make accessibility productive and sustainable. Companies must see the skills of people with disabilities as strengths that can power the rest of the company, or else they will not see good outcomes.

The model revealed gaps at Microsoft and offered a picture of what “good” looks like. As a result, the company incorporated inclusive hiring policies that draw talent from underrepresented groups, such as people with autism, many of whom pursue science, technology, mathematics, and engineering careers. The commitment to accessibility must be embedded into all aspects of the hiring process, including accessible online application forms. The company determined that the interview process was problematic for people with autism, so it created an academy approach that brings talented candidates with autism into a setting that allows them to demonstrate their skills. As a result, Microsoft has hired some excellent people with disabilities and learned from them how to be more inclusive.

Once it has talent from people with a range of disabilities, a company can use the principles of inclusive design to embed their expertise into company processes and policies. Inclusive design involves recognizing an area of exclusion and resolving the barriers that lead to that exclusion. Fixing a problem that appears to affect only a small minority can lead to benefits for many. Instead of guessing what people with disabilities might need, inclusive design incorporates the people with disabilities in determining what is required.

Ms. Lay-Flurrie provided several examples of technology products designed with and for people with disabilities that have expanded access to many, such as an adaptive gaming controller (developed through an annual hacking convention that Microsoft hosts) that does not require the use of thumbs. It was designed for veterans who were not able to use their thumbs but was later recognized as a good device for young kids. Microsoft improved its accessible computing products and made them easier to find and use in its most popular applications, such as the accessibility checker for Office documents. Options such as closed captioning and transcripts are now widely available for free in Microsoft products and used by many.

Advances in artificial intelligence (AI) and machine learning have driven many accessible technologies. Ms. Lay-Flurrie observed that it is crucially important to invest in AI and harness human capabilities to move forward, with attention to issues of ethics, privacy, and confidentiality. Microsoft has funded research to accelerate AI, but progress has been slow, and

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

the research landscape is sparse. Ms. Lay-Flurrie emphasized the need to democratize data by incorporating more voices and images into databases that are used for machine learning. She highlighted some Microsoft research on the potential use of eye-tracking technology to expand communication capacity among people with amyotrophic lateral sclerosis. Microsoft's Project Tokyo blends AI and artificial reality in a way that could, for example, help blind people better understand the nonverbal communication of others.

Ms. Lay-Flurrie concluded that people with disabilities are the experts on their needs and capacities. Embedding their understanding into methods and strategies is key to unlocking the potential they offer. Inclusive design is vital, she added. Finally, more data and more collaboration are needed to unleash the capacity of AI. Working together can accelerate the journey toward accessibility, Ms. Lay-Flurrie stated.

Discussion

Several commenters asked how they could get involved with Microsoft to share data and promote advancements in accessibility and AI research. Ms. Lay-Flurrie replied that her field desperately needs more data to build better products, and she invited individual researchers to contact the company or her directly with their ideas.

Dr. Cernich asked to what extent wearables are useful in capturing data from people with disabilities. Ms. Lay-Flurrie said people with disabilities must be part of the design process to ensure that wearables are feasible and comfortable to use. Affordability is also a key factor for people with disabilities, and the industry can do more to keep costs down. Dr. Cernich added that all sectors find it challenging to provide people with disabilities with the assistive technology they need.

Perspectives

Moderator: Alison Cernich, Ph.D., NICHD

Consumer Advocacy and NIH Rehabilitation Research Advancements: A Historical Perspective

Peter Thomas, J.D., Advocate, Powers Pyles Sutter & Verville PC

Mr. Thomas described the creation of NCMRR as a result of efforts that began in the 1980s, headed by researchers and other advocates who felt rehabilitation research needed to carve out a presence at NIH, ideally as a freestanding Center or Institute. In 1990, Congress authorized the creation of NCMRR within NICHD because of that Institute's focus on human development while recognizing that the research agenda cuts across multiple disciplines. The authorization incorporated proposed legislation to support development of advanced technology orthotics and prosthetics (the Claude Pepper Act for Amputees).

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

The legislation also created the National Advisory Board on Medical Rehabilitation Research (NABMRR), made up of 12 researchers or scientists and six people with disabilities. The inclusion of consumer members was novel and breathed new life into creating a research agenda relevant to the ultimate end users. The Americans with Disabilities Act also passed in 1990, and the disability community's mantra "nothing about us without us" informed the composition of the board.

NCMRR's published its first research agenda in 1993, following extensive deliberation about the application of the medical model to the research plan. The Center's slogan, Focus on Function, continues to reflect its goals. The Center grew substantially and scaled up efforts into the late 1990s, drawing attention to rehabilitation research at a time when some questioned whether rehabilitation was a legitimate area of science. Other Institutes and Centers (ICs) have since become more involved in rehabilitation research, but NCMRR remains the NIH lead.

In the late 2000s, advocates, clinical organizations, and research groups led a renewed surge of interest in NCMRR and rehabilitation research across federal agencies and formed the Disability and Rehabilitation Research Coalition (DRRC). In response to the DRRC's request for increasing NIH's focus on rehabilitation research, NIH Director Francis Collins, M.D., Ph.D., called for a review of the research landscape. A blue-ribbon panel assessed the work of the previous 20 years and published their evaluation and recommendations in 2012, many of which were implemented by NIH. For the first time, NCMRR was allocated a dedicated budget (a fixed percentage of NICHD's extramural research budget), allowing for long-term planning.

The DRRC worked with Congress to ensure that NIH, through NCMRR and the other ICs, would expand and maximize coordination and visibility of rehabilitation science at NIH. Legislation also required NCMRR to hold periodic conferences and develop an NIH-wide rehabilitation research plan every 5 years. The legislation required standardization of definitions used for data collection as a way to overcome barriers to exchanging research.

In recent years, NIH has experienced another resurgence in rehabilitation research, with nearly all ICs participating, coordinated by the trans-NIH Medical Rehabilitation Coordinating Committee. Mr. Thomas acknowledged Dr. Cernich's excellent leadership of NCMRR and her work within NICHD and across NIH as well as with other federal agencies, including the National Institute on Disability, Independent Living, and Rehabilitation Research; the National Science Foundation; the U.S. Department of Defense (DoD); the U.S. Department of Veterans Affairs (VA); and others that conduct rehabilitation science.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Transforming Barriers into Doors: A Case Study on the Impact of NCMRR on a Rehabilitation Research Career

Edelle Field-Fote, Ph.D., PT, FAPTA, Shepherd Center; Chair, NABMRR

Dr. Field-Fote outlined her path from physical therapist to rehabilitation research scientist. The interdisciplinary, person-centered nature of physical therapy gave her valuable skills to apply to research. Dr. Field-Fote pointed out that NIH's 2016 Research Plan on Rehabilitation mentioned training repeatedly throughout, underscoring that training is a priority.

Dr. Field-Fote received a T32 training grant to pursue doctoral research in movement science, focusing on the role of spinal circuits in producing bilaterally coordinated behavior when there is no input from the brain, using a preclinical model of turtle scratching behavior. She realized that some of the patterns of walking she observed were applicable to other species and to certain types of disability. At the same time, very good evidence that rehabilitation is among the most valuable approaches for some types of disability was emerging.

Supported by a K01 grant, Dr. Field-Fote then began to study the role of sensory motor inputs on walking function in people with spinal cord injury (SCI). She determined that neuromodulatory inputs directed at spinal circuits can serve as a valuable adjunct to locomotor training. For her first R01 grant, Dr. Field-Fote incorporated the insights she had received from study subjects, who were most interested in whether interventions improved function and reduced spasticity. Through a comparative study of locomotor training techniques, she determined that training-related neuroplasticity of spinal circuits is associated with improved walking function after SCI, raising questions about what other circuits could be modulated with training and other approaches.

With a second R01 award, Dr. Field-Fote sought to improve hand and arm function in people with SCI, demonstrating again that neuromodulation can be a powerful adjunct to training. Understanding the optimal dose of neuromodulation remains a challenge. Dr. Field-Fote pointed out that pharmaceutical research spends a lot of money to clarify dose response, but rehabilitation research does not. She has since been focusing her research efforts on clinically accessible neuromodulation for improving movement and integrating it into real-world clinical practice.

Dr. Field-Fote emphasized the importance of funding to train future rehabilitation research scientists. In addition to research grants, NCMRR supports several initiatives to promote training, such as the Training in Grantsmanship for Rehabilitation Research program and the Medical Rehabilitation Research Resource (MR3) Network. Dr. Field-Fote concluded that her

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

training enabled her to pursue a great career, and she encouraged others to seek out similar opportunities through NIH and NCMRR.

The Future of NCMRR

Theresa Cruz, Ph.D., Director, NCMRR

Dr. Cruz appreciated the history of NCMRR provided by Dr. Thomas. She acknowledged that the current administration stands on the shoulders of the first NABMRR, which invited people with disabilities to shape the research agenda and established NCMRR's vision of focusing on function. Dr. Cruz believes NCMRR leads the field in three areas: resources, partnerships, and communication.

In terms of research funding, Dr. Cruz encouraged participants to let her know what kinds of support mechanisms are still needed. Not every project fits into the framework for an R01 award, and Dr. Cruz asked for input on how NCMRR can be more forward-thinking and develop other mechanisms to support innovative approaches. NCMRR established an early-career research award to bolster the pipeline of investigators and help early-career scientists to gather data to support an R01 application. (Dr. Cruz noted that because of the disruptions to research caused by the COVID-19 pandemic, NCMRR is extending the timeline for early-career investigators to take part.)

Other resources for rehabilitation research include the Training in Grantsmanship for Rehabilitation Research program, which pairs applicants with mentors who help them hone their grant applications, and the Association of Academic Physiatrists' Rehabilitation Medicine Scientist Training Program. The MR3 Network provides expertise and offers facilities, webinars, consultations, and pilot funding. Two efforts at NIH to identify common data elements so that researchers can compare and share their findings—a federal interagency working group on standardizing data in limb loss research and, with NINDS, a community-led effort to create neurorehabilitation common data elements—are underway.

Partnerships are incredibly important, said Dr. Cruz, especially for a small organization with limited resources. NCMRR forges partnerships within NIH and across the federal government to expand its reach. For example, NIH's Pathways to Prevention program is planning a workshop on the question of whether physical activity improves the health of people who use wheelchairs, sponsored by NCMRR, NINDS, and the NIH Office of Disease Prevention. The NIH–DoD Limb Loss and Preservation Registry is a novel contract with the Mayo Clinic to gather data on various aspects of limb loss and limb differences.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Dr. Cruz praised NCMRR's communication office, noting that she hopes to highlight more grantee science in future communications through NCMRR's press releases, social media accounts, and newsletter. She also aims to increase attention to rehabilitation research through more lectures and other mechanisms. Dr. Cruz thanked all those who crafted and supported this conference. She noted that all the presentations and posters from this conference will be archived for 1 year and available on demand.

Discussion

Dr. Cernich asked what transitions posed the biggest challenges for people coming into this area of research and how NCMRR is thinking about new ways to bring in and support researchers. Dr. Cruz responded that the pipeline always has leaks; for example, researchers who cannot secure a tenured position typically leave the field. The pandemic has complicated the pathway for early-career researchers, so NCMRR is allowing them more time to take advantage of its transitional funding mechanisms. NCMRR and other ICs also offer funding for people who are not following a traditional career model.

Dr. Field-Fote pointed out that at one time, people questioned whether rehabilitation research was a “real” science. Now there is no doubt about the value of the research. Discoveries have led to new devices and revealed the plasticity of the nervous system, making it a very exciting time for research.

Dr. Cernich asked what challenges the field faces now. Mr. Thomas said NCMRR and its partners have made tremendous progress and that virtually all the ICs conduct some rehabilitation research. He hoped the recent surge in enthusiasm and commitment to the field would continue. Mr. Thomas said there have been dramatic improvements in the technology for prosthetics and orthotics. He urged the field to be mindful of the next step: ensuring that these new products are covered by insurance and accessible to the people who need them. Mr. Thomas acknowledged that such concerns are beyond NIH's purview but must be recognized.

Translational Research: Research Plan Theme E

Moderator: Craig McDonald, M.D., University of California, Davis

Therapeutic Intermittent Hypoxia as a Primer for Motor Recovery After SCI: A Balancing Act
Randy Trumbower, Ph.D., Spaulding Rehabilitation Hospital

Dr. Trumbower described the progress of research on therapeutic intermittent hypoxia from basic science to clinical application. More than 20 years ago, scientists identified a complex cascade of acute intermittent hypoxia (AIH)–induced plasticity and spinal motor nuclei that cause upregulation of brain-derived neurotrophic factor, which ultimately increases neuron strength and results in functional improvements in breathing capacity. Investigators found that

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

upregulation of brain-derived neurotrophic factor through AIH is necessary and sufficient to elicit the long-term facilitation of respiratory drive in rodents with high cervical lesions that compromised breathing. They went on to determine that AIH could also restore limb function in rats with spinal cord lesions.

Dr. Trumbower said investigators gained a new appreciation for how therapy in one motor or sensory system applies to others, such as diaphragmatic breathing involving other muscles and neurons. Further studies in rats revealed that AIH was most potent when combined with training and had no effect on rodents with no training. These findings suggested that AIH enhanced performance and might be useful as pretreatment for task-specific motor training.

Early studies recognized the need to balance the potential benefits of AIH against the potential risks of chronic hypoxia (e.g., sleep apnea). A first-in-humans trial comparing AIH alone and with training among people with SCI demonstrated profound improvements in walking among those who received AIH and no serious adverse events from the treatment. Dr. Trumbower posited that AIH accelerates performance. He noted that it is more effective in boosting the results of training than as standalone therapy. Notably, the beneficial effects did not persist for all of the study subjects, so investigators doubled the duration of treatment, yielding dramatically better results.

Despite the promising discoveries, approximately 30% of subjects did not have improvements in walking speed or distance with daily AIH, suggesting that the benefits may be attenuated by competing mechanisms. Further testing aimed to block the constraints to certain receptor pathways by administering caffeine before AIH, resulting in improved performance compared with AIH or caffeine alone.

Dr. Trumbower concluded that AIH alone and with training improve neuroplasticity and may have potential for broad use as an adjunct to other rehabilitation approaches for people with SCI. The future of such treatment depends on determining whether there are physiological markers that make people more or less responsive to treatment and whether there are conditions that influence the safety and efficacy of this treatment, such as medications, genetics, inflammation, or sleep-disordered breathing.

Using Biology to Inform Precision Medicine Approaches for Musculoskeletal Care

Gwen Sowa, M.D., Ph.D., University of Pittsburgh

Dr. Sowa pointed out that despite advances in musculoskeletal care, outcomes have not improved significantly. She is working to understand unique patient phenotypes that can guide care in a rational way. The musculoskeletal system degenerates over time through natural

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

aging, with resulting tissue changes, and the changes are biologically distinct from those that result from injury. A comparison of vertebral disc damage caused by injury versus aging demonstrates significant differences in gene expression of growth factors and inhibition of breakdown, among other distinctions.

Imaging is frequently used to assess musculoskeletal conditions, but findings correlate poorly with patients' experience of pain. In people with low back pain who do not have serious underlying conditions, advanced imaging increases the likelihood of interventions but does not affect functional outcomes. A new approach is needed.

Basic science indicates that that different levels of mechanical loading affect spine cartilage cells—in some cases dampening inflammation and enhancing regeneration but in other cases having the opposite effect. Dr. Sowa explained that mechanical loading (e.g., exercise) can be reparative or detrimental, depending on the stage of degeneration and individual biology. One goal is to identify a surrogate marker that can be translated into humans to determine who will respond positively to mechanical loading.

Using animal models, investigators applied magnetic resonance imaging (MRI) to see musculoskeletal degeneration; they also sampled blood over time for key biomarkers. One biomarker revealed significant differences between injured and uninjured animals. The biomarker appeared as much as 3 weeks before MRI results identified the injury. Dr. Sowa said the findings indicate that blood-based biomarkers are more sensitive than imaging and might be capable of exposing active disease and not just injury.

In humans, investigators identified some biomolecules that were associated with patients' self-reported experience of low back pain and some combinations of biomolecules that were associated with pain scores, depression, patients' description of pain, and matrix turnover. The biomarkers yielded modest associations but were significantly better than MRI. Investigators are now bringing the results from the human biomarker studies back to the laboratory to assess whether the biomarkers are relevant to overall pathophysiology and can be used to guide treatment.

Dr. Sowa and colleagues compared patients who responded to steroid injections for low back pain with nonresponders and found that responders had higher circulating levels of neuropeptide Y (NPY). Circulating NPY was also associated with changes in pain and mobility scores. A study of exercise in people with spinal stenosis also found that responders differed from nonresponders based on NPY. A laboratory model further confirmed that response was influenced by NPY, regardless of whether the disc was subject to inflammation or mechanical stress.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Back in the clinical setting, a study of people with osteoarthritis of the knee revealed a telling biomarker that is involved in cartilage turnover. The higher the expression of the biomarker, the more painful it was to walk for 45 minutes continuously (compared with three 15-minute bouts of walking). Such findings could be applied to titrate exercise and limit the harm of mechanical loading.

Dr. Sowa said it is unlikely that a single biomarker that can guide treatment of musculoskeletal conditions will be identified, but she proposed bringing together all of the available measures to inform predictive tools. Combining clinical findings, such as response to therapy, with genetic data can help investigators tease out the mechanics with the eventual goal of target therapies.

As part of NIH's Helping to End Addiction Long-termSM (HEAL) Initiative, Dr. Sowa and colleagues are creating extensive phenotypes of patients with low back pain that will combine biological data with behavioral data (e.g., sleep, activity, alcohol use, psychological profiles) and biomechanical information gathered from imaging and wearable devices. An interdisciplinary team of researchers will bring unique perspectives to bear, with the goal of identifying unique phenotypes that can be targeted for treatment through adaptive clinical trials.

Discussion

Sue Mukherjee asked whether the participants had traumatic or nontraumatic SCI. Dr. Trumbower explained that his clinic sees a wide range of patients with SCI. All of the participants in the AIH trials had some form of incomplete SCI, both traumatic and nontraumatic. For the studies, it was necessary to ensure that participants had SCI injury that was not progressing, regardless of the type.

Sarah Donkers asked whether people with certain comorbidities were excluded, such as those with sleep-disordered breathing. Dr. Trumbower said that sleep-disordered breathing is a major issue among people with SCI. In recent studies he published, people with sleep-disordered breathing had a moderate response to AIH. People with severe disorders, such as severe sleep apnea, were excluded from the study.

Andrea Domenighetti asked whether epigenetic profiling is more efficient than individual genetic profiling. Dr. Sowa said her study would use epigenetic profiling. Big data sets require sophisticated modeling to find a needle in a haystack, and that is the direction in which research should head. The use of genetic biomarkers is a huge step forward, and adding epigenetic information allows investigators to look at how things are expressed, which can be used for prediction.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Katie Butera asked how to address the challenges of collecting phenotype data and interpreting biomarkers in the rehabilitation setting. Dr. Sowa said the ability to collect biosamples at the point of care is increasing. To interpret the data, she and others are working with data analysts to create user-friendly dashboards that practitioners and patients can use to evaluate the predictive capacity of the biomarkers.

Dr. McDonald asked both speakers to describe the challenges of conducting translational research during a pandemic. Dr. Sowa said her institution had a facility-wide plan for restarting research, instilling confidence in the research participants. Investigators did as much as they could remotely, including talking with participants on the phone about the conduct of the study, and are using telemedicine more. Recruitment efforts are using registries more and advertising on public transportation less. Dr. Trumbower said the AIH therapy involves breathing a modified aerosol, so investigators are modifying the delivery systems to ensure the systems are not contaminated. Investigators are also conducting surveys to understand how study participants are coping with the pandemic and how researchers can facilitate participants' access to their healthcare providers.

Pragmatic Trials: Research Plan Theme D

Moderator: Thubi H. A. Kolobe, PT, Ph.D. FAPTA, University of Oklahoma

Pragmatic Research: How It Can Complement, Extend, and Challenge How You Do Science (and Increase Your Impact)

Jennifer Stevens-Lapsley, PT, Ph.D., University of Colorado Denver

Traditional research trials are slow and expensive, and the findings often are not relevant to clinical settings. It takes an average of 17 years for research findings that identify effective interventions to translate into practice, and only 14% of such research ever reaches that stage. Adding in the time before the research begins (e.g., for grant applications and pilot studies), the actual translation time can be more than 20 years. Dr. Stevens-Lapsley said that pragmatic research will increase the likelihood of translation and that combining it with implementation science will speed up the process.

Unlike controlled trials, which limit the variables and patient selection to achieve ideal circumstances, pragmatic trials evaluate interventions under normal conditions, among diverse subjects recruited from clinical settings. Dr. Stevens-Lapsley stressed that research is conducted along a continuum and that explanatory research is still needed to understand how an intervention works. She noted that the process is not always linear and that it is never too soon to think about the ultimate step of implementation. Dr. Stevens-Lapsley outlined the fundamental differences between randomized and pragmatic controlled trials, noting that pragmatic trials aim to inform clinical decision-making and allow for some customization. She

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

emphasized that pragmatic trials are an important addition to science and do not diminish the role of basic science or randomized trials.

The second Pragmatic Explanatory Continuum Indicator Summary (PRECIS2) tool enables investigators to evaluate the pragmatism of published literature or to demonstrate a pragmatic approach in the context of a funding application. Using the tool, an investigator assigns a score (1–5, from least to most pragmatic) to each of a number of domains, such as participant eligibility requirements, study setting, and organizational infrastructure involved. For example, a study that recruits a narrow population of people likely to respond to the intervention could receive a score of 1, while a study that involves all the adult patients who visit the clinic and have the condition for which the intervention is indicated could receive a score of 5. Dr. Stevens-Lapsley walked through some examples of research, applying the PRECIS2 to achieve a pragmatism score.

Among the barriers to more pragmatic research is the disconnect between academic research and clinical practice. Academic advancement often relies on publishing research in scientific journals, and there is little emphasis on broader communication of the findings. In general, practicing clinicians do not learn about new interventions from journals. To speed translation, academic researchers must think about what stakeholders (e.g., the end users of interventions) value from the outset, not just what the researcher wants to test.

Real-world pragmatic research requires an understanding of the research environment, organization and patient characteristics, the leadership culture of an institution, the interaction of programs in the context of implementation, infrastructure, and sustainability. Too often, the scientific field assumes that if a body of evidence is created, practitioners will adopt the best practices, but that is not always the case. Building in more pragmatic research will improve translation, she concluded.

From Pragmatic Trials to Practice—Principles of Implementation Science

Janet Bettger, Sc.D., FAHA, Duke University

Dr. Bettger observed that many effective medicines, toolkits, interventions, and policies are never fully incorporated into practice because even translational research models fail to pay attention to the final steps to achieve long-term implementation. To achieve NIH's mission, Dr. Bettger proposed a goal of translating 80% of findings that describe effective interventions into practice within 3 years.

Implementation research is the scientific study of the development and use of strategies to adopt and integrate evidence-based health interventions into clinical and community settings

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

to improve individual outcomes and benefit population health. Dr. Bettger summarized some key terms, emphasizing the need to identify effective strategies that can ensure that interventions are put in place.

Implementation science assumes that education alone is not sufficient. Uptake requires provider buy-in. The intervention must fit into the workflow and clinical context. Outcomes of implementation research address various facets:

- Implementation: acceptability, adoption, appropriateness for the target population, costs, feasibility, fidelity, penetration, sustainability
- Service: efficiency, safety, effectiveness, equity, patient-centeredness, timeliness
- Client: satisfaction, function, symptomatology

Dr. Bettger summarized two implementation studies as examples of different designs. In one, investigators compared three real-world strategies for implementing a telephone hearing screening test for adults. In another, investigators evaluated several methods for delivering physical therapy to people who had had total knee arthroplasty. In both cases, the interventions themselves were known to be effective. In the hearing screening study, investigators assessed which approach to screening was most effective. In the physical therapy study, investigators knew that cost was a barrier and sought to learn which implementation approach was least costly while also being feasible and acceptable.

By better understanding specific barriers to implementation, researchers can identify the strategies likely to be effective in overcoming them. Some investigators have categorized behaviors related to implementation and mapped them to strategies, which can be tested. For example, Dr. Bettger explained, investigators can assess the differences between organizations that do and do not adopt a practice guideline to identify potential levers to improve adoption. One framework for moving evidence into practice is RE-AIM, which stands for reach, effectiveness, adoption, implementation, and maintenance. Dr. Bettger noted that maintenance of interventions over time should not be overlooked.

Implementation should be taken into account even before definitive trials reach their conclusion and should, in fact, be considered in the design of the intervention. Researchers and practitioners should work with community partners to ensure that interventions are adopted.

The COVID-19 pandemic spurred many shifts in strategies for reaching patients. Researchers in 12 countries identified technology as a barrier to patients receiving rehabilitation services. Individuals have different capacities for using telehealth, and the implementation of tele-rehabilitation varies by organization and provider. Dr. Bettger said the pandemic offers an

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

opportunity to gather much-needed data on implementing tele-rehabilitation broadly. Because of the pandemic, efforts should be made now to scale up tele-rehabilitation to learn what works for whom. Dr. Bettger identified some useful resources for learning more about implementation science:

- [Training Institute for Dissemination and Implementation Research in Cancer modules](#)
- [Institute for Implementation Science Scholars](#) (Washington University in St. Louis)
- [Implementation Science Exchange](#) (tutorials, trainings, and sample grants)
- [Implementation Science](#)
- [AcademyHealth Dissemination and Implementation Conference](#)

Discussion

Dr. Kolobe asked how important stakeholders are to implementation science and pragmatic research. Dr. Stevens-Lapsley responded that academics often work in silos and are surprised that their results do not translate into practice. It is imperative that outside stakeholders be involved at the outset in informing research goals and design, as Ms. Lay-Flurrie described in her keynote address. A number of resources are available to support training in pragmatic research and implementation science, such as the MR3 Network, the Learning Health Systems Rehabilitation Research Network ([LeaRRn](#)), and the National Institute on Aging's [Imbedded Pragmatic Alzheimer's Disease \(AD\) and AD Related Dementias Clinical Trials \(IMPACT\) Collaboratory](#).

Lauren Hinrichs asked how clinical trialists can think about implementation before they have established the efficacy of an intervention. Dr. Bettger responded that thinking about such questions early on is important for ensuring that research benefits patients. At the least, investigators can set up a framework to examine implementation as the research moves forward. In the process of developing interventions, researchers make critical decisions about which population to address, which providers to engage, and what theory of action to apply. The intent of the intervention shapes thinking at the earliest stages, so there are opportunities early on to involve stakeholders and patients and to ask what outcomes are meaningful for them.

Dr. Bettger pointed out that investigators can apply a proven framework to evaluate the characteristics of an intervention that affect implementation, such as the processes and the training required for use in a clinical setting, the cost to patients, and who pays for it. She added that there are guidelines for documenting such decisions, which will help accelerate the work for others.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Steven Wolf asked about the extent to which the perceived need to generate revenue per unit of time in clinical rehabilitation settings impedes the cooperation and collaboration needed to reach the pragmatic trial stage. Dr. Stevens-Lapsley noted that Medicare used to pay for 21 days of physical therapy in a skilled nursing facility following total knee arthroplasty, regardless of the actual time required, so facilities had little incentive to take part in trials. However, as Medicare moved to a patient-driven payment model, the landscape shifted, and interventions that could speed up the rehabilitation process became attractive. Healthcare payment policies have a significant impact on translation and implementation.

Mary Khetani asked whether NIH is receptive to proposals that include hybrid designs and what strategies applicants should use when proposing them. Dr. Stevens-Lapsley said efforts are underway to educate application reviewers and journal reviewers and editors about pragmatic research and implementation science, but there is always a lag before such knowledge is fully incorporated into a review. She noted that NCMRR's research priorities reflect increased awareness of the value of such work. Dr. Bettger suggested applicants consider where they submit proposals; NIH's recently established review panel on healthcare delivery and methodology would be a good fit for this type of research. She also recommended becoming familiar with the language, rationale, and goals of a given area of research and reflecting them in the application.

Edward Hurvitz wondered whether reviewers would downgrade proposed studies that are not classic randomized trials. Dr. Stevens-Lapsley said that over time, such bias would diminish. In the meantime, she urged applicants to target applications to the appropriate review panel and provide good rationales for their proposed work. Dr. Bettger noted that randomized trials can complement pragmatic and implementation research, and investigators might want to move back and forth among the different frameworks as the needs of the research dictate.

Regenerative Rehabilitation: Research Plan Theme E

Moderator: Arthur English, Ph.D., Emory University

Resonance: Optimizing Regenerative Rehabilitation's Impact, Efficiency, and Sustainability

Fabrisia Ambrosio, Ph.D., M.P.T., University of Pittsburgh

Using the analogy of acoustic resonance, in which all the parts of an instrument contribute to amplify its sound, Dr. Ambrosio described the concept of regenerative rehabilitation as the combination of regenerative medicine and rehabilitation to maximize outcomes. The Alliance of Regenerative Rehabilitation Research and Training (AR3T) seeks to accelerate the pace of discovery by investing in cutting-edge research across the continuum from basic science to translation.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Refining regenerative rehabilitation requires understanding how forces affect stem cell responses. One laboratory seeks to understand how tenocytes respond to various mechanical loads in their native environment. It uses a novel tendon model that shows changes in gene expression in response to mechanical loading, which is expected to inform the prescription of rehabilitation methods for tendon injuries.

Stroke research has advanced further in the pipeline. ClinicalTrials.gov currently lists nearly 90 studies on stroke involving stem cells. A 2014 paper outlined key considerations for clinical trials of cellular science for stroke treatment: identifying an optimal candidate for stem cell therapy, determining the ideal timing of administration, and assessing the types, amount, and timing of other rehabilitation in conjunction with stem cell therapy.

AR3T supported a study of a rodent model of ischemic stroke that combined stem cell therapy with exercise. The study found that exercise and stem cell therapy each contributed to improvement independently, but the combination of the two resulted in less improvement than either alone. Another mouse study developed a more complex exercise challenge that more closely mimics the specific training involved in rehabilitation, which might be useful for better understanding the combination of exercise and stem cell therapy. Other investigators found that an ultrasound-guided soft robot that controls the delivery of a mechanical load enhanced functional recovery in animal models. These studies offer potential for translation into meaningful therapeutics.

Dr. Ambrosio proposed pursuing research at the atomic scale, through the convergence of quantum mechanics and biology. For example, European sparrows migrate by sensing and responding to alterations in earth's geomagnetic field. Quantum biology has a wide range of implications for species with such sensitivities. One research group demonstrated that humans have strong, specific responses in the brain to changes in magnetic fields, even minor changes. Investigators now have proof of the principle that quantum phenomena can regulate cell responses within a biological system.

Dr. Ambrosio said her laboratory brings various disciplines together, such as theoretical physics and bioengineering, to evaluate questions such as whether stem cells exploit the body's magnetic field to direct cells to the site of injury. The findings could lead to development of novel regenerative rehabilitation techniques, such as magnetic therapy combined with stem cell treatment. There is enormous potential to coordinate the state of the art in the field and emerge with powerful new approaches, Dr. Ambrosio concluded.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Developing Treatments for Duchenne Muscular Dystrophy Using Regenerative Rehabilitation Tools

David Mack, Ph.D., University of Washington

Dr. Mack made the case that research is already succeeding in combining regenerative medicine and rehabilitation medicine techniques into mechanisms for restoring function. Investigators have introduced mechanical and electrical stimulation that promotes differentiation and maturation of stem cells in tissue. The investigators have also integrated mechanical and biophysical cues to maximize outcomes, demonstrating that research is now combining stem cell biology, bioengineering, and biomaterials.

Dr. Mack's laboratory created a three-dimensional heart model to increase understanding of molecular and cellular responses to biomedical signals in vitro that also accounts for behavior at the tissue level, unlike other models. Investigators use induced pluripotent stem cells harvested from the urine of a patient with Duchenne muscular dystrophy (DMD) to create a model that captures the individual patient's genotype—a technique Dr. Mack refers to as "disease in a dish." The model provides a platform for high-throughput screening and drug development, yielding results that are more likely to work in a given patient because they have been tested in a model based on that patient.

The mechanics of dystrophin are not well understood, but it protects against stress-induced damage. The deficiency of dystrophin that characterizes DMD leads to fibrosis, systolic dysfunction that causes extensive cardiac remodeling, and eventually heart failure, typically in the early teens among people with DMD. Dr. Mack further detailed the molecular pathology of DMD that leads to a downward spiral in function among these patients.

Dr. Mack explained that the three-dimensional model allows investigators to measure aspects such as force and electrical stimulation in a way that two-dimensional models do not (because they sit on a hard, plastic surface). The three-dimensional model also better mimics the cell-to-cell contact of live tissue. Using the three-dimensional model, investigators can assess in real time the kinetics of contraction and relaxation and, through calcium-sensitive dyes, see normal heart rhythms and histology, for example. This advanced visualization allows them to see the impact of a drug. The engineered heart tissue used in the models can demonstrate the typical effects of DMD.

The ability to create a mature model in a dish that resembles the actual disease in a patient is key to advancing regenerative rehabilitation. Products are being developed to further incorporate mechanical strain and electrical stimulation, which are hallmarks of rehabilitation therapy, into disease models. One such product is a cyto-stretcher.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Discussion

Stacey Dusking said research in the field often focuses on restoring capacity to adults, but participants want to know whether AR3T would support research into “generative” medicine in the early stages of development. Dr. Ambrosio said AR3T has not received many applications on the topic but that it is an area of great interest. There is also interest in imprinting—that is, how various mechanical cues applied during development manifest as effects only seen in adulthood. Dr. Mack said his colleagues are beginning studies involving mechanical and electrical stimulation in embryonic development with the goal of mimicking the native embryonic milieu. He noted that it is important to learn what happens in normal embryonic development and apply those lessons to fool cells into regenerating themselves.

Todd Cade asked what other interventions are being proposed in the stem cell cardiomyocytes besides gene therapy. Dr. Mack said there are very promising data emerging from studies of cardiac stem cell transplantation into the heart following myocardial infarction that show the cells engraft and beat synchronously with native cells. Additional work is underway on gene editing.

A participant asked presenters to comment on the biggest impediments to achieving resonance between regenerative and rehabilitation medicine. Dr. Ambrosio said that better preclinical models of rehabilitation are needed. The common approach of evaluating treadmill running after pathology does not adequately mimic clinical treatment. The field should better demonstrate rehabilitation protocols in preclinical models so that more can be learned about optimal timing, intensity, and frequency, ultimately making the results easier to translate. Dr. Mack pointed out that the field will soon need investigators interested in developing new, personalized rehabilitation strategies for people whose conditions were improved or cured by gene therapy.

Community and Family: Research Plan Theme B

Moderator: Barbara Lutz, Ph.D., R.N., University of North Carolina Wilmington

Social Networks in Rehabilitation Research: Evidence, Challenges, and Opportunities

Amar Dhand, M.D., Ph.D., Brigham and Women’s Hospital

Dr. Dhand explained that social isolation is demonstrably detrimental to health and that stroke survivors are particularly vulnerable to isolation. Better outcomes are seen in people who have a lot of social support, particularly those who experienced moderate to severe stroke, for whom rehabilitation participation is especially important for recovery.

Dr. Dhand and colleagues mapped the “social connectome” by asking individuals to identify the members of their social network and categorizing the contacts by their role in the individual’s

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

life, whether that is someone from whom the individual seeks advice, social contact, or support. The researchers then depicted the connections and the strength of the ties to the individual, as well as looking at how the various contacts connected with each other. The resulting map quantified the strength of ties and the density of the network. Dr. Dhand went on to evaluate how social networks affect recovery among people who had a stroke and how the networks changed over time.

In the study, which involved mostly people with mild stroke, the subjects' social networks usually shrank by about one person following the event, which is a significant change from baseline. At the same time, the density of the network increased—that is, the people in the network become more interconnected. The networks tended to include more family members after stroke, fewer people who smoke, and fewer people who do not exercise. Notably, the size of a person's social network at the time of stroke was an independent predictor of physical function at 3 and 6 months after stroke. Also, people whose network contacts had weak ties to each other tended to get to the hospital sooner when a stroke occurred. Dr. Dhand said that those unconnected contacts provided more novel information to practitioners than strongly connected contacts did.

Dr. Dhand pointed out that the research excluded many people with large strokes that affect language and alertness, and he welcomed suggestions on how to include them. He also seeks to understand how to help people develop larger social networks with more healthy contacts, because those networks enhance recovery. His laboratory is pursuing two potential mechanisms: Social Bit, a wearable sensor that detects interaction, and Hometeam, a platform for activating a social network.

The Social Bit is worn on the wrist and captures the amount of time spent talking with other people (but does not capture the content of conversation). Dr. Dhand is planning to study its use in stroke survivors in the hospital, in rehabilitation, and at home to assess whether it accurately detects social interaction and the patterns of interaction. He believes the Social Bit could be used to coach people on increasing their social interaction and might have broad applications for counteracting social isolation.

The Hometeam platform provides education on caregiver support and how to increase one's social network after an acute illness. Using a chat feature, the patient's healthcare provider interacts with the patient and contacts to provide information, support, and encouragement. Dr. Dhand said the initial experience in which he engaged in frequent text chats with a patient and her contacts was promising.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Discussion

Raeda Anderson asked about the role of network churn in the research findings and whether the researchers limited the number of contacts included in the network. Dr. Dhand said the published data describe the churn, but individuals' networks did not change significantly over the 6-month period of the study. Researchers allowed subjects to name as many contacts as they wanted but sought information about only the first 10 people identified.

Ken Wood wondered whether the Social Bit distinguishes positive from negative social interaction. Dr. Dhand said researchers are currently focused on whether the tool accurately measures the duration of interaction as a first step. They are also gathering observational data on whether the interactions are deep or casual and positive or negative, and Dr. Dhand hoped that the Social Bit could eventually provide that information.

Paul Gross asked whether similar research on social connection is being conducted for rehabilitation from elective surgery or chronic conditions, such as cerebral palsy. Dr. Dhand responded that he is participating in a study involving people with Down syndrome. He was not aware of anyone doing this kind of research among people who had elective surgery.

Julie Schwertfeger asked how patient-reported outcome measures were integrated into studies. Dr. Dhand said his research uses NIH's Patient-Reported Outcomes Measurement Information System (PROMIS) as the main option for assessing the influence of the social network on physical function. Patient-reported outcomes are intimately integrated into the conceptual modeling and research design.

Sandeep Subramanian asked about the role that the severity of motor and cognitive impairment plays in, for example, texting among people who suffered stroke or traumatic brain injury. Dr. Dhand said he had not read any literature on the effect of these injuries on texting, but his clinical experience reveals mixed effects. Some patients who suffered severe stroke have told him they prefer texting to in-person socializing because they feel less vulnerable or exposed at home than outside the home. However, Dr. Dhand recognized that some patients may have specific motor and cognitive limitations that make it difficult to text. He is working with technology providers to enable Hometeam to accommodate people with differing abilities.

Yu-Lun Chen asked how research using the Social Bit would control for nonverbal interactions, particularly among stroke patients with language difficulties. Dr. Dhand said the Social Bit would capture paraverbal sounds (but not silent, nonverbal interactions), which could improve rehabilitation results for people with aphasia.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Dr. Lutz asked whether the shrinking of an individual's social network after a stroke results in more burden on the individual's caregiver. Dr. Dhand said responsibility increases for the caregivers, particularly the lead caregiver. Having a larger network means that the responsibilities are distributed across more people. Dr. Dhand said research might look at whether the caregiver's burden can be quantified in the context of network size and the changes in a network over time.

Dr. Lutz wondered whether the tools to address social isolation could be translated to other settings, such as senior retirement communities or assisted living facilities. The COVID-19 pandemic also offers an opportunity to look at the effects of social isolation, particularly among vulnerable populations. Dr. Dhand said he is awaiting a response to a proposal to study a pandemic-specific mechanism for assessing social isolation. The ramifications can be seen indirectly by the 30% drop in the number of people presenting at the hospital with heart attack or stroke, a change that Dr. Dhand believes is directly related to social isolation and limited social networks.

Devina Kumar asked whether interaction with therapists and healthcare providers is considered socializing in Dr. Dhand's research. Dr. Dhand replied that in his research on stroke patients, the participants determined who was included in the social network, based on who they consider an important source of advice, social contact, or support, so all types of providers can be included.

Dr. Lutz asked whether texting with caregivers and patients through the Hometeam platform is very time consuming. Dr. Dhand said the initial effort did not take scalability or economy into account, and texting did take time. He added that it was very rewarding to communicate with patients and their network of friends and family, especially when there was an opportunity to provide support that moves the network forward. Future iterations would include several members of the research team so the time commitment could be distributed across team members.

Friday, October 16

Welcome

Walter Koroshetz, M.D., Director, NINDS

Dr. Koroshetz welcomed the participants and described how the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative will inform rehabilitation research. The Initiative seeks to develop technologies to monitor, map, and modulate neurocircuits. The goal of rehabilitation among people with neurological injuries is to improve the brain's ability to

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

rewire, recover, or compensate or to provide devices to optimize function. Dr. Koroshetz hoped that within the next 10 years, the BRAIN Initiative would map the neurocircuitry and allow investigators to visualize rewiring and develop ways to enhance it. He believes that circuit-based rehabilitation will be part of an exciting future. Already, some people are using neurocircuits to control computers. Dr. Koroshetz said that the future of neurology is in recovery and rehabilitation.

Sensory and Communication Rehabilitation: Research Plan Theme C

Moderator: Elizabeth Skidmore, Ph.D., OTR/L, FAOTA, University of Pittsburgh

Investigating Functional Visual Performance and Neuroplasticity in Cerebral Visual Impairment
Lotfi Merabet, O.D., Ph.D., M.P.H., Harvard University

The number one cause of pediatric blindness and visual impairment today is brain damage; 20 to 30 years ago, the most common causes were diseases, such as rubella and retinopathy of prematurity, and the results were categorized as ocular visual impairment. According to Dr. Merabet, teachers in schools for blind and visually impaired children acknowledge that the curricula and skills of the past no longer apply to the changing population, and new mechanisms for understanding and addressing cerebral visual impairment (CVI) in learning are needed. CVI is characterized by unique, higher-order visual processing deficits.

Visual function describes how well the eyes and visual system perform in terms of standard assessments of acuity, contrast, and visual field, but these tests do not reflect how people see things in the real world. Functional vision measures performance in real-world scenarios and is difficult to measure objectively. Both work together, but the relationship is unclear, especially in people with brain damage. Investigators are now using virtual reality to assess visual function and functional vision in a controlled and measurable way to understand how the two relate.

Dr. Merabet described a range of virtual reality scenarios to compare vision and function in children with ocular visual impairment or CVI. For young children, the task is to pick a specific toy out of a toy box. For adolescents and teens, the task involves identifying a specific person in a crowded hallway. Investigators can manipulate the scenario by modifying color, contrast, and visual clutter. They can also track where the viewer looks and for how long, data that provide insight into the user's level of difficulty with the task.

The virtual reality tests demonstrate that children with CVI can have good visual acuity but impaired processing, especially as the demands of the task increase. Manipulating the environment—for example, using a brighter color to draw attention to the target—can make tasks easier. The findings from these tests can be applied in classrooms to identify what helps children with CVI see and learn better.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Dr. Merabet stressed the importance of distinguishing visual function from functional vision. Furthermore, the causes of visual impairment should be distinguished, because the approaches to education differ depending on the cause. Dr. Merabet concluded that virtual reality is a novel approach to characterizing functional visual assessment with high ecological validity.

Prosthetic Limbs and Sensory Restoration

Dustin Tyler, Ph.D., Case Western Reserve University

Dr. Tyler summarized a number of research advances in restoring sensation in people who use prosthetic hands and feet. His team has outfitted several people with hand prostheses that have electrodes and multiple contacts that connect to different parts of the nerves to restore hand sensation. Some subjects have been using the prostheses for years with no complications. Investigators have successfully recreated tactile sensations down to the tip of the finger, allowing the user to experience varying levels of intensity. Dr. Tyler said that the brain adapts to the sensations and that, by manipulating the electrodes, researchers have been refining and optimizing the quality of sensations.

Proprioception is an individual's sense of the body in space, and improving sensation—for example, increasing the sensitivity of touch in a prosthetic hand—allows the individual to use a hand without having to look at it. Better sensory input allows the user to modify the amount of pressure applied to objects and to move more precisely. These benefits can reduce fatigue in the user and even decrease the amount of energy required of batteries used in the prosthetic device.

Dr. Tyler pointed out that perception is a combination of sensory input and expectations. When the two clash, the result is an optical illusion. When they match, an individual is more likely to identify a sensation correctly. However, visual input without corresponding tactile input can be distracting. Dr. Tyler described a series of experiments demonstrating that the expectation of what something should feel like affects the individual's experience of a sensation. In people using prostheses, artificial information can be integrated into the body schema and sensory intake.

People using the hand prostheses from Dr. Tyler's laboratory demonstrated sustained improvement on measures of quality of life, such as self-efficacy and interaction with others. The participants reported more sensory input over time and began to experience sensations in ways that correlate with normal biological sensations. Dr. Tyler said he just received approval to begin a study of a prosthetic system that involves an implanted device connected by leads to an external hub that communicates with the wearer. He concluded that touch is connection and that humans embodying technology is the future.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Impact of AI and Machine Learning on Communication Sciences and Rehabilitation

Rupal Patel, Ph.D., CCC-SLP, Northeastern University

Dr. Patel indicated that the digital revolution affects every sector. AI, machine learning, and automation are leading to the creation of more data and new tools and collaborations between humans and machines, which could fundamentally change basic science and the field of rehabilitation. Through wearable sensors, for example, researchers can now capture data at scale (thanks to miniaturization and improved sensor fidelity) and record behavior from a large, diverse population in real-world settings. The pandemic has forced researchers to consider how to collect data remotely, which could have the benefits of mitigating investigator bias and overcoming barriers to research participation. Automated tools and multidimensional analysis speed up data analysis and reveal patterns and trends while also providing more objectivity. Dr. Patel said the field still lags in sharing data across large groups.

In the clinical setting, individuals are benefitting from improved monitoring that allows for personalized interventions, as well as assistive technology that improves function and quality of life. As technology captures more data over time and more normative data, identifying early, subclinical symptoms will become possible, enabling early intervention. Advances in biomarkers can illustrate changes in response to therapy.

Dr. Patel noted that speech recognition technology paved the way for Siri, Alexa, and other devices and applications that can respond to natural voice commands. Innovators are finding creative ways to use these systems to improve communication—for example, through apps that can help an individual verbally fill out a form, report symptoms, or tell a story—and even to provide companionship for people who are isolated.

The voices of these devices are generic, whereas humans have unique voices. Given the reliance on voice applications by people with communication disorders, Dr. Patel's team created Vocal ID, which uses AI and machine learning to break down recorded speech into the elements needed to generate a digital voice. Through crowdsourcing, Dr. Patel and colleagues collected audio from 28,000 people. Using advanced tools, the team cleaned up the sources to create a databank of voices.

Dr. Patel explained how Vocal ID generated a voice for Maeve, a 9-year-old girl who can produce sounds but not speak. Maeve's sister recorded thousands of sentences, which were combined with Maeve's sounds to create a unique voice. Now, when Maeve speaks through assistive technology, the voice is unique to Maeve. Dr. Patel said ownership of one's voice increases communication and participation.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Voice ID also aims to facilitate voice preservation for people with conditions that take away speech. The company helps people record their voices into a bank so that their own voices can be used later as the source of a digital voice. The company is working with universities in the United States, the United Kingdom, and Canada to capture people’s voices before their capacity for speech deteriorates. Dr. Patel noted that in less than 10 years, creating a voice went from taking more than 40 hours of recording to taking just 1.5 hours.

Dr. Patel urged participants to think about the application of research and technology not just to human functions but to the individual person. Voice applications can be used to engage, build trust, increase adherence, and gather feedback. Dr. Patel hopes research will embrace what new technology has to offer to improve function and quality of life.

Discussion

Dr. Skidmore asked the presenters to identify some priorities for future research that will bring transformative change in how sensory and communication processing is studied and how applications in the field are developed. Dr. Tyler hopes the field will start bringing together the various elements of research and findings from individual laboratories into a broader context to identify and fill the gaps. He stressed the importance of seeing rehabilitation as the effective integration of all the parts of a system. Dr. Patel added the need for collaboration to gather and exchange more data more quickly in support of iterative research.

Dr. Tyler appreciated Dr. Patel’s attention to the relationship between humans and technology, noting that the interaction offers many opportunities to collect various forms of data; for example, gaming could give insights on reaction time. Dr. Tyler also noted that game developers do an excellent job of bringing together all the parts of a system to create realistic games. Dr. Patel added that researchers are beginning to use games and the technology of gaming—as demonstrated by Dr. Merabet’s use of virtual reality.

Mobility: Research Plan Theme A

Moderator: Stephanie Deluca, Ph.D., Virginia Polytechnic Institute and State University

Advances in Pediatric Outcomes: Neuromodulation and Rehabilitation—Past, Through COVID-19, and Beyond

Bernadette Gillick, Ph.D., M.S.P.T., PT, University of Minnesota

Dr. Gillick described a range of research underway involving neuromodulation. Her laboratory assesses the results of noninvasive brain stimulation in children with brain lesions. In pediatric research, particularly in early brain injury, the goal is to spur recovery as the brain is still developing. Dr. Gillick said interventions should strive toward providing a functional future.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Transcranial magnetic stimulation provides a visual depiction of brain activity during movement, and researchers can use it in conjunction with physical training. Neuromodulation has been demonstrated to be safe, feasible, and effective in children and adults. Trials demonstrated that repetitive transcranial magnetic stimulation combined with constraint-induced therapy improved hand function in children who had had a stroke. In some of the study subjects, the uninjured side of the brain controlled both sides of the body, and these subjects did better with the intervention than those who did not have preserved cortical cross-function.

In infants, researchers found that the younger the baby, the more likely that noninvasive brain stimulation would elicit motor-evoked potential (i.e., electrical signals) in the upper extremities. Current research is using transcranial direct-current stimulation (TDCS), stratified according to whether the subject's cortical circuitry is typical or atypical. So far, both groups have demonstrated increased motor-evoked potential in response to TDCS. Dr. Gillick said work to determine whether noninvasive brain stimulation can provide predictive information about cortical motor-evoked excitability is underway.

In response to the COVID-19 pandemic, Dr. Gillick's institution put out guidelines for research. In the meantime, researchers determined that there is a market for in-home TDCS and launched a study to assess the feasibility of at-home neurorehabilitation in children with cerebral palsy and limited mobility during the pandemic. The study began by monitoring how well families and caregivers did with electrode placement. Also in response to the pandemic, researchers conducted an online survey that confirmed that individuals experienced disruptions in rehabilitation and mental health services that may have an impact on their health status and increase the burden on families and caregivers.

Dr. Gillick's laboratory is planning a study of infants affected by perinatal stroke. She hopes that the study will provide information on recovery and integrity of the corticospinal tract and reveal whether biomarkers can predict the risk of cerebral palsy after perinatal stroke.

Intuitively Controlled Devices for Improved Mobility

Levi Hargrove, Ph.D., Shirley Ryan AbilityLab

Dr. Hargrove gave an overview of devices for mobility and the challenges that users face, focusing on prosthetic lower limbs. Passive devices that use springs and dampers are generally well engineered and work for many people. More sophisticated versions include computers that help control movement. Motorized devices include an energy source that propels the prosthesis. A number of products aimed at improving users' mobility are in various stages of development, most of which involve a rigid device that is easy to move (although soft robotic devices are emerging).

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

New smart devices have many sensors that measure the load of walking, the reaction force, and other factors that can be used to enhance mobility in different situations. Smart prostheses can collect neural information from the user so that the device recognizes certain shapes—such as ramps or stairs—and responds accordingly. The more advanced the device, the more smoothly the user can negotiate changing terrain. With direct neural control, the user thinks about the movement and the device responds. Navigating transition points—such as reaching the top of the stairs and then walking normally—is critical to function.

Dr. Hargrove noted that his team begins by testing devices on healthy, young people with good mobility, many of whom adapt quickly to the prostheses. The group is now engaging older amputees, who have found that with some adjustments, they can walk smoothly and comfortably without having to look at their feet.

Researchers are moving into studying exoskeletons, several of which are on the market now. Dr. Hargrove pointed to one product in testing that assists with hip joint movement and could be used for rehabilitation or to help older people stay active. He noted that device research is resource intensive, with many people involved in direct observation of a single participant to understand how the device feels and what the user needs. Beyond the function of the device, the usefulness of a device depends on users incorporating the prosthesis into their lifestyle and body image.

Normalcy Fallacy: Reimagining Mobility for Scientific Discovery and Innovation

Kat Steele, Ph.D., M.S., University of Washington

Dr. Steele stated that current definitions of what constitutes normal limit the field: “Normal” walking is not best for all bodies in all environments, and it is time to expand the vision of mobility. Motion analysis technology has enhanced understanding of how humans move, allowing assessment of the impact of surgery and mechanical interventions. Yet the assessments rely on normalcy and thus do not take the neurofunction of people with conditions such as cerebral palsy into account.

The Gait Deviation Index (GDI), for example, distills a lot of data into an easy-to-interpret metric for comparing individual performance against a population average. Research shows that only half of people experience clinically significant improvement in GDI score after orthopedic surgery.

People with cerebral palsy consume twice as much energy walking as other people, resulting in significant fatigue. It is not known why they use so much energy, and no treatments significantly reduce the fatigue. Furthermore, following surgery, there is no association

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

between changes in GDI score and energy levels. Some people have improved energy but no change in GDI score, leading Dr. Steele to question whether they adopt a different, less taxing technique for walking.

All the models used in kinetics, kinematics, and related fields are based on normalcy (e.g., in terms of bone shape and joint movement) that lead to misinterpretation of individual movement. By creating individualized models, researchers can begin to see unique and optimal patterns of movement that go beyond the bounds of normal.

Dr. Steele described some areas where the concepts of mobility and inclusion are being applied to push back against the narrow confines of normalcy. Real estate listings have only recently begun to include accessibility features make home buying easier for people with disabilities. Some apps for maps and directions identify potential access barriers and offer alternatives. Dr. Steele called on the rehabilitation community to play an active role in imagining new solutions to enhance accessibility.

Low expectations and setting “normal” as a goal are significant impediments to people with disabilities. Dr. Steele pointed out that some children with disabilities are denied mobility devices because of concerns that the devices will impede development. More understanding of how mobility devices can support development is needed. If the goal of therapy is mobility across the lifespan, customized solutions need to be considered.

Dr. Steele encouraged the participants to consider how the assessments and metrics they use are tied to assumptions of normalcy and might be limiting their understanding. She asked that the participants evaluate the space around them and the tools they use to evaluate the challenges they might pose and the adaptations they might require. More people with disabilities are needed in the fields of engineering and rehabilitation, and more people in those fields should be trained in inclusive design. Finally, Dr. Steele urged participants to learn more by visiting the website of the [Center for Research and Education on Accessible Technology and Experiences](#), a multidisciplinary partnership that champions accessibility in all sectors.

Discussion

Dr. Field-Fote said the adult TDCS literature shows tremendous variability in physiologic and functional outcomes. She asked whether Dr. Gillick sees less variability in pediatric populations, and if so, why. Dr. Gillick responded that the younger the subject, the higher the level of neuroplasticity. She believes that variability persists across the lifespan. Trials might use the same intensity, duration, and frequency of TDCS for all participants, but the effectiveness might depend on the lesion burden, location, and other individual factors. Computational modeling is

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

needed to better understand the specific needs of individuals. Dr. Gillick echoed Dr. Steele, noting that function may be atypical.

Scott Delp, Ph.D., asked Dr. Hargrove to expand on what prosthetic controllers quantify. Dr. Hargrove replied that the goal is to optimize the comfort of the prosthesis for the user, often by hand-tuning the parameters. The first step is ensuring the user can walk at a comfortable speed, stopping and starting safely. Adjustments are then made to enhance speed and reduce metabolic cost, although Dr. Hargrove noted that he has not been able to minimize metabolic cost for all of his subjects, which may be related to weight, among other factors. He added that controllers allows for optimization but are limited by the hardware.

Dr. Delp asked Dr. Steele to address the role of individuals in defining their goals as a means to guide precision rehabilitation. Dr. Steele responded that the field has some good tools for asking rehabilitation participants about their functional goals related to specific interventions. Incorporating those goals as outcomes is important for rehabilitation and surgical interventions. Dr. Steele also suggested setting higher expectations. From Day 1, she said, the full spectrum of options should be presented to anyone who has an injury, so that person can envision a range of possibilities and set goals that allow a wide variety of activities.

Data Science: Research Plan Theme F

Moderator: Eric Perreault, Ph.D., Northwestern University

Reproducibility in Rehabilitation Research and How Data Science (and Open Science) Can Help
Sook-Lei Liew, Ph.D., OTR/L, University of Southern California

Dr. Liew said multiple causes lead to the inability to reproduce a scientific experiment as described in the literature and to replicate the results reliably. Causes include underuse of reproducible methods, inconsistent recordkeeping or reporting by team members, positive publication bias, and underpowered studies. Adopting tools from data science can improve reproducibility, and open science approaches can lead to better replicability.

Dr. Liew offered some simple data management approaches: Use consistent file naming protocols and formatting so that data files are machine readable; document the variables, assumptions, and data sources used; and use version control software to keep track of the data generated and the analyses. Dr. Liew gave examples from the Center for Reproducible Neuroimaging. For one publication, available in print and online, the author shared the results and analysis along with the code used to generate the analysis, allowing users access to the data set and the tools to reproduce the research. Several resources applicable to rehabilitation research are available:

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

- [Mobilize Center](#) at Stanford University
- [Center for Large Data Research and Data Sharing in Rehabilitation](#)
- 2019 American Society of Neuroradiology Symposium: Reliability and Reproducibility in Neurorehabilitation Research
 - [Hands-on tutorials and slides on GitHub](#)
 - [Center for Reproducible Neuroimaging](#)
 - [2020 NeuroHackademy](#)
- [Coursera](#), [Udemy](#), and other online learning sites

Open science principles can overcome positive publication bias and publishing limitations by enabling investigators to share large data sets, codes, and protocols and to make these items publicly available. This approach might be used to incorporate different types of data into an analysis, enable trainees to evaluate existing data, or test hypotheses in a large population. The following data sources are related to rehabilitation research specifically and funded by NCMRR:

- [Center for Large Data Research and Data Sharing in Rehabilitation](#): many types of data, including health services research (e.g., medical records) and retrospective study-specific rehabilitation data
- [Archive of Data on Disability to Enable Policy and Research](#): retrospective study-specific rehabilitation data
- National Center for Simulation in Rehabilitation Research [OpenSim](#) Community
- [SimTK](#): free motion simulation toolbox and trained models for different populations

More broadly, the [Human Connectome Project](#), [UK Biobank](#), and NIH's [All of Us Research Program](#) are all rich data sources. Within research fields, numerous sources offer data and tools for public use. Dr. Liew recommended reaching out to individual researchers to request use of their data and seeking ways to make the exchange mutually beneficial (e.g., by organizing the data into an archive that could be published). Some organizations offer data sharing grants to cover the time and effort of archiving existing data. Dr. Liew hoped participants would consider data management and sharing as part of the effort to improve science overall.

Accelerating Rehabilitation Science with Big Data

Scott Delp, Ph.D., Stanford University

Ubiquitous, inexpensive wearable devices (e.g., Fitbit, Apple Watch) can provide massive amounts of detailed data. Dr. Delp described a collaboration with Azumio, a smartphone app that captured motion data from 2 million people worldwide. Researchers sought to determine whether the distribution of physical activity within a population affects overall public health

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

and how the built environment affects physical activity. Moreover, they wanted to know whether the findings from the app were trustworthy and how to distinguish signals from noise.

By comparing demographics between the app users and databases from the Centers for Disease Control and Prevention, the researchers confirmed that the app users were fairly representative of the U.S. population. Trends identified in the app data, such as weight gain and activity decline, were similar to known trends.

Dr. Delp and colleagues found that populations demonstrating “activity inequality”—in which some people get a lot of exercise and many get no exercise—correlated with obesity in the United States, Canada, and Australia. China and Japan have low levels of activity inequality and low rates of obesity. The researchers further mined the data to conclude that activity inequality predicts obesity across age, gender, and income status. By layering data on walkability in U.S. cities, they demonstrated that more walkable cities have lower rates of activity inequality and obesity. Combining the data allowed investigators to look closely at activity levels throughout the day and stratify those findings by gender and income.

Dr. Delp said the Center for Reliable Sensor Technology–Based Outcomes for Rehabilitation (RESTORE), part of the MR3 Network, seeks to create a worldwide network of researchers collecting and sharing data gathered largely from wearables. It provides a portal for sharing data and offers tools for analysis (primarily through machine learning), virtual office hours with experts, and a knowledge base of best practices. RESTORE provides small grants for researchers to generate pilot data and a fellowship program through which experts can share their expertise with investigators new to the field. RESTORE just released a [tool](#) that allows users to collect key biomechanical measures from gait videos and [OpenSense](#) for gathering biomechanical data from wearables.

Discussion

Dr. Steele asked what data science training would be useful for physical therapists, occupational therapists, and other allied health professionals and how engineers, designers, and software developers can make tools that are more accessible to people in these fields. Dr. Liew said a lot of learning happens in the laboratory setting among peers, but she would like to see more formal education on data science and computer programming. She is seeking funding to provide entry-level data science education. Dr. Liew also recommended finding a mentor who can help with troubleshooting. She noted that many user-friendly tools are widely available online.

Dr. Perreault asked for more details on how activity inequality and walkability are measured. Dr. Delp responded that activity inequality is measured in the same way as income inequality,

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

using the Gini index, and walkability is a standardized metric that was overlaid on the data set gathered from the wearables. The walkability score is specific to walking and generalized to cities, so it does not capture good data by neighborhood, Dr. Delp cautioned.

Dr. Perreault asked what new data management tools are needed to move rehabilitation research forward. Dr. Liew replied that, at the basic level, rehabilitation researchers can ensure that their data are organized, maintained, and stored in formats that are amenable to AI and machine learning approaches, ideally with researchers taking data management into account when designing protocols. She also called for harmonization of data collection and storage so that the resulting information can be pooled and shared.

Margaret Nosek wondered how groups that have little experience with data sharing can come together to harmonize data collection and storage. Dr. Liew said that collaboration is needed and should reflect the consensus of the community about what kind of data are needed and what is feasible. The Stroke Recovery and Rehabilitation Roundtable, for example, has published consensus papers on common data elements and measures that should be used across the field. Dr. Liew suggested starting a conversation with peers about some basic measures that everyone could agree to collect.

Dr. Perreault asked how to ensure that massive data sets gathered from wearables are representative and of good quality. Dr. Delp replied that algorithms are useful for sifting good from poor data. The data set he uses does not have information on disability or ethnicity at the individual level, so its representativeness is difficult to assess.

Dr. Perreault asked how the pandemic affected activity levels. Dr. Delp hypothesized that activity inequality has increased overall, but he has not yet been able to assess the data.

Dr. Perreault asked whether any databases of human movement based on wearables are freely accessible. Dr. Delp replied that the Mobilize Center at Stanford University and SimTK have free databases and tools to analyze the data. He noted that organizing data to support sharing is a lot of work, and investigators are reluctant to put in that work if they do not get a publication credit for it. Some investigators are apprehensive that others will find errors in their data. Dr. Delp said that when the supporting data are shared in conjunction with published findings, papers have much greater impact. He added that publishing data can save years of research time and accelerate the field, so the benefits are significant.

Dr. Liew agreed that the processes involved in sharing data are tedious and complicated but that the results have tremendous impact. Researchers who share their data do get some criticisms of the data and lots of requests for additional data elements, but the overall impact

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

of sharing the data is substantial. Dr. Liew gave an example of a published data set being leveraged by students who cannot collect new data because of the pandemic. She proposed more incentives for sharing data, such as small grants to support such efforts. Dr. Liew noted that more journals are publishing data sets, so investigators can get publication credit for sharing their data.

Dr. Perreault asked what teaching resources are available to advance the concepts discussed. Dr. Delp said that for people who are already familiar with data science, there are many good software tools and online resources available. Getting people comfortable with data science, however, is a challenge. Dr. Delp said that in the long term, every undergraduate student should be required to take computer science. In the short term, institutions should develop more entry-level classes.

Dr. Liew added that entry-level learning for some can be as simple as having an experienced person willing to help a trainee get started and troubleshoot the initial problems, although this approach is resource intensive. She strongly advocated for teaching basic computer programming, so that everyone understands the principles of how computers read and store data. Dr. Perreault observed that enrollment in computer science classes is going up exponentially across the country.

Future of Rehabilitation

Moderator: Theresa Cruz, Ph.D., Director, NCMRR

Placebo: From Mechanisms to Implications for Clinical Trials

Luana Colloca, M.D., Ph.D., M.S., University of Maryland

Dr. Colloca distinguished placebo effects—changes in neurobiological responses and clinical outcomes—from placebo responses, such as biases and concurrent interventions that influence outcomes. In studies, the best way to separate the two is to include an arm in which no interventions are used. Dr. Colloca seeks to understand how the placebo mechanism can inform clinical trials. Pain research has confirmed that humans can experience the placebo effect as a result of suggestion and prior experience. Dr. Colloca explained that activating learning and expectations can stimulate different circuits in the brain, some of which are key to modulating pain responses. She explained that the placebo effect is a tool for better understanding the process of modulation and how outcomes can be modulated.

In a laboratory setting, conditioning and learning are powerful mechanisms for creating placebo effects. Dr. Colloca described a study in which participants received morphine to block induced pain and later received a placebo, which produced a morphine-like response to the induced pain. She noted that the findings could be relevant for helping chronic opioid users taper off the

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

drug. Brain imaging studies demonstrated the role of learning in the placebo effect. People whose brains showed more activation during the training phase showed larger placebo effects.

The placebo effect can be stimulated by observation of another participant receiving a painful or nonpainful stimulus. Brain imaging revealed that the more communication, or functional connectivity, between certain areas of the brain, the more likely the participant was to experience placebo-induced analgesia.

To understand the role of genetics, Dr. Colloca looked at the single-nucleotide polymorphisms for opioid, dopamine, and cannabinoid receptors, which show up in different combinations and magnitudes in relation to placebo effects. She determined that genetics alone cannot predict response to a placebo. Other psychological and clinical components also shape the response. Further studies confirmed that expectation also plays a role and can be manipulated.

Researchers assessing patients with chronic orofacial pain found that the placebo effects are similar across sex, race, and age. Dr. Colloca emphasized that any treatment can induce a placebo effect that is modulated by expectations. For example, the mechanism used to administer a drug and how the administration is explained can affect the patient's response. Therefore, it is important to be careful about how interventions are communicated to participants so that the research team is consistently managing expectations.

Dr. Colloca said that researchers who run clinical trials should try to understand that what participants and providers expect can jeopardize the outcome. The language, procedures, and questions posed should be as standardized as possible to prevent participants from experiencing adverse events related to expectations.

Scientists should establish a study arm of people who receive no intervention and incorporate findings from that arm into the analysis. They should further explore cluster and modeling approaches to understand how to predict placebo response and conduct replication studies as needed. More data sharing will reveal the phenotypes of placebo responders.

Clinicians can take advantage of the placebo effect by aligning their patients' expectations with the anticipated therapeutic outcome. Clinicians should consider the context of the intervention—from the smell and color of a drug to the words used when therapy is delivered. Video is a powerful tool for informing patients about the nature of placebo effects.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Advancing Trials Through COVID-19 and Phase II

Albert Lo, M.D., Ph.D., Brown University and President, American Society of Neurorehabilitation

Dr. Lo said his perspective is influenced by his years working with a biopharmaceutical maker and his academic career, which included work with the VA. He noted that the pandemic has posed barriers to research but also offers an opportunity to rethink how clinical trials are conducted. Recommendations from a June 2020 article for preserving the integrity of trials during the pandemic include informing study participants about changes to the trial, winnowing down the outcomes to those of highest priority, implementing alternatives to in-person visits, and modifying in-person visits to reduce the risk of disease exposure for participants and staff.

Further guidance on conducting clinical trials urged investigators to weigh the risks to patient safety of continuing or discontinuing a study. It might be necessary to modify a protocol to continue a study. Dr. Lo said there are indications that FDA is willing to work with researchers to come up with acceptable solutions. The pandemic has forced researchers to consider or accelerate new mechanisms, which Dr. Lo believes can improve the research enterprise and the delivery of clinical care for the future, such as the following:

- Virtual and hybrid trials that incorporate telemedicine, remote monitoring, in-home clinician visits, and mobile treatment units
- New technology for validating outcomes measures gathered through remote devices
- Streamlining study design to focus on the most important outcomes and data needed to answer the research question

These approaches will reduce the burden on participants and improve access to care. They might even increase participation of minorities in research trials and save money.

The failure to translate study results into clinical practice stems from the failure of studies to progress beyond Phase II trials. Part of that shortcoming is that investigators may use different markers to assess outcomes in Phase III—for example, in a rehabilitation trial, using a surrogate marker of range of motion in Phase II and demonstrated participant capacity in Phase III. To illustrate barriers to translation, Dr. Lo compared two large studies of robotic rehabilitation devices published approximately 10 years apart. Although the later trial was larger and benefited from some advances in technology and trial design, the outcomes were not substantially better and did not translate well in terms of capacity. Reviewers concluded that robotics trials should be targeted toward people most likely to respond, through better selection of study participants, including the use of predictive biomarkers. Dr. Lo said that, rather than seeking pragmatic results, research should focus on designing the best trials to test

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

the hypothesis and identifying what works in a clearly defined population, then expanding from there.

In conclusion, Dr. Lo observed that robotics research can be adapted to progress during the pandemic. Robotic devices are compatible with a virtually supervised environment and are useful for reproducing simple, repetitive movements. It might be possible to create robots good enough to provide users with a basic level of motor power and coordination that could then be enhanced through in-person visits with a rehabilitation specialist.

Mechanistic Studies, Clinical Trials, and the Future of Both
Daniel Corcos, Ph.D., Northwestern University

Dr. Corcos made the case that research to understand mechanisms is as important as clinical trials and can inform clinical practice. He advocated for basic and mechanistic research, especially as a pursuit for junior investigators. To illustrate, Dr. Corcos outlined the career of someone whose work on people with chronic pelvic pain began with neuroimaging studies about the mechanisms involved and progressed to a clinical trial of an intervention to reduce the pain.

The Study in Parkinson's Disease of Exercise (SPARX2), a Phase II clinical trial, determined that people with Parkinson's disease who were not yet taking medication for the condition could exercise safely at high intensity, and those who did so did not see progression of the disease. These findings, combined with earlier research on monkeys demonstrating the effects of exercise on the brain, were the basis for proposing a Phase III trial. That study, SPARX3, aims to establish whether high-intensity exercise can be a first-line therapy for people recently diagnosed with Parkinson's disease to slow the progression of disease.

Given the poor track record of Phase III trials for neurodegenerative disorders, the SPARX3 investigators engaged with grant program officers to modify the study design. It was determined that the primary outcome variable should be measured at 12 months rather than 6 months and that the intervention study should take place over 2 years. Dr. Corcos posed the following question: If the study fails to show a difference in the progression of disease between the intervention group and the control group (similar people exercising at moderate rather than high intensity), is it a failed clinical trial? While statisticians and others might conclude it is, Dr. Corcos urged the rehabilitation community to take a principled position on the interpretation of the results of large clinical trials, even when the results are not supported by the superiority hypothesis. He added that medical ethicists will have a larger role in future rehabilitation research in cases in which the individual study participant's experience is positive but does not meet the threshold for superiority.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

SPARX3 will assess a panel of inflammatory and neurotrophic biomarkers that might yield a sensitive biomarker from blood samples. It will evaluate a set of sensitive, functional outcome measures and gather genetic data from participants. Researchers will compare responders and nonresponders. The differential responses introduce variance that makes it difficult to interpret results of clinical trials broadly, but understanding the distinctions might reveal new information. Dr. Corcos noted that interim power analysis will be conducted and the number of participants increased as needed.

Dr. Corcos recommended basic research to identify mechanistic biomarkers. While clinical trials should be conducted with rigor and transparency, the clinical trial framework should not be applied to studies that are not intended to change clinical practice. There is much work to do to smooth the transition from Phase II to Phase III trials. Clinical trials can be designed to provide valuable information even if the superiority hypothesis fails. Researchers should develop adaptive statistical models for interim assessments to determine whether trials should be discontinued or modified. The duration of funding should be consistent across NIH and should acknowledge that 5 years is often not enough time for a study to achieve the desired results.

Discussion

Dr. Cruz asked whether Dr. Colloca observed gender differences in the placebo studies. Dr. Colloca said she explored how sex can modulate placebo responsiveness, what hormones are involved, and sensitivity, because women are more sensitive to pain than men. She found that women experienced larger placebo effects, independent of hormones or pain sensitivity. Women have a larger expectation of effect, which contributes to a larger placebo effect.

Dr. Cruz asked about the role of phenotyping in simplifying studies. Dr. Lo said that if researchers can identify those most likely to respond, studies could use fewer participants. Better understanding the phenotype might also enable researchers to decrease the amount or frequency of outcomes data collected.

Carolee Winstein asked Dr. Corcos to expand on how clinicians should interpret a failed trial in the context of clinical practice. Dr. Corcos responded that if, for example, SPARX3 were to show some benefits for both high-intensity and moderate exercise, clinicians would have to consider how to present the findings so that patients can decide which approach is best suited to their lifestyle and preferences.

Yang Wong asked Dr. Colloca to discuss her work using virtual reality tools to study the components of placebo. Dr. Colloca replied that her laboratory is using virtual reality to explore how individuals can improve pain tolerance—for example, through distraction.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Dr. Cruz asked how to ensure that people with disabilities are included in more pharmaceutical trials. Dr. Lo said researchers are more receptive to including people with disabilities than they used to be, especially if such inclusion is relevant to the mechanism of action of the intervention studied. He added that now is the time for more researchers to ask why a given population should not be included in the study. Dr. Cruz pointed out that NICHD advocates that more women, pregnant women, lactating women, pediatric populations, and people with intellectual, developmental, or physical disabilities be included in research.

George Wittenberg said that using the terms “responder” and “nonresponder” might create an artificial dichotomy when, in reality, responses may fall along a spectrum. Dr. Colloca said that in some trials, there are clear criteria that distinguish response from nonresponse. Dr. Lo agreed that in some cases, there is a spectrum of responses, but he noted that there are also people who do not respond at all. Dr. Corcos agreed that great care should be taken when creating such a distinction. As understanding advances, it might be possible to better distinguish differences in response to dose and to identify endogenous mechanisms at play. The goal is to pick apart the reasons behind responsiveness or nonresponsiveness for the sake of moving forward with treatment options without categorizing people in ways that do not benefit them.

Wrap-Up

Theresa Cruz, Ph.D., Director, NCMRR

Dr. Cruz thanked the financial supporters, staff, and planners of this conference, as well as the partners who shared resources in the exhibit hall. She thanked all of the speakers, moderators, and poster presenters for providing incredible scientific content and the contractors and technical and logistical staff for ensuring that the conference stayed on track.

Dr. Cruz encouraged the participants to continue to weigh in on the future of NIH rehabilitation research through [NICHD.ideascalegov.com](https://www.nichd.nih.gov/ideas). The Rehabilitation Research Plan is available there and will be open for public comment until November 15, 2020. Participants are also welcome to submit ideas via email.

In conclusion, Dr. Cruz pointed out that shifting to a virtual conference had allowed many more people to join the conversation, and inclusion is what rehabilitation is all about. Nearly 1,200 people took part, which is more than twice the capacity of NIH’s conference center. Dr. Cruz looked forward to a time when the field could safely meet in the same physical space.

Appendix: Highlights from the Networking Lounge Discussions

Moderators invited participants to provide comments on the draft research objectives for each theme, as described in the [request for information](#). The following summarizes some of the suggestions raised via discussion conducted through the online chat room.

Theme A: Rehabilitation Across the Lifespan (October 16)

Topics to Consider

- Aging with a childhood-onset disability, such as cerebral palsy
- Chronic pain in adults with disabilities (e.g., cerebral palsy) and prevention or management of secondary musculoskeletal manifestations and associated pain, especially ongoing preventive management
- Understanding the complex interactions over time of the influence of altered forces on the developing musculoskeletal system, plus the additional impact of aging
- Premature biological aging in people with disabilities
- Integrating models of aging of populations impacted by pediatric-onset disabilities
- Research using sensor methodology in children (current hardware is too heavy and too loud)
- Transition to adulthood
- Pediatric guidelines and knowledge for how to intervene and when, especially during growth and development

Research Approaches

- To enhance diversity, partner with established leaders in diverse communities.
- Offer incentives, such as tools related to the research that people can use in their homes and fair compensation for time engaged in research.

Other Considerations

- There is a tendency to focus on the health topics that lie near the bottom of Maslow's pyramid rather than thinking about the self-actualization for people with disabilities.
- We spend too much on how fast and how far and not enough on how satisfying or how meaningful.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Theme B: Community and Family (October 15)

Topics to Consider

- Better understanding of what individuals with disabilities, their families, and their carepartners are seeking, particularly in terms of self-management. (There was a lot of enthusiasm for replacing the word “caregivers” with the term “carepartners.”) Start by identifying self-management needs and how they differ among and between different subsets of the population.
- How families react to disability and long-term impact on independence for children born with disabilities
- How social networks tie into a self-management model
- Assessing the needs of the carepartners
- Role of the health of the caregiver
- Executive function issues are a challenge to research in the spina bifida community. Nonverbal learning disabilities are often not addressed but have a huge impact on learning.
- Well-being of young people ages 16–24 who are born with a disability transitioning from school to work environments—their supports, success rates, caregiver involvement, and mental health
- How families can best address issues of food security, finances, access to groceries, food preparation, and eating behaviors

Research Approaches

- Community-based participatory research or stakeholder engagement at a minimum
- Including the populations and their carepartners in the research design
- Real-world evidence and more pragmatic study designs
- Pragmatic research at different points across the lifespan
- Empowerment use of home-based resources (telehealth and wellness counseling)
- Improving health literacy, educating laypeople on how to observe simple signs of health decline, providing access to tools, technology, and expertise to support home and wellness, community living

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Theme C: Technology Use and Development (October 16)

Identifying Needs and Solutions for People with Disabilities and Their Families

- Ask, “What do you use to help you with (activity or task) now?”
- Check in as a regular part of treatment plan by asking, “Is this working for you?” and “What do you wish were different?”
- Use a satisfaction survey at the end of research studies to gather information on how to better tailor studies to meet the needs of patients and families.
- Hold routine meetings with the clinicians who provide orthotics and prosthetics to learn about the feedback they get from their patients.
- Check in regularly with participants through structured and unstructured data collection.
- Use data from patients and clients in developing the outcome assessments that gauge success and identify needs.

Integrating User Feedback

- Feedback from users is critical to understanding usability and optimizing devices.
- See the Cybathlon model, a sporting event in which people with disabilities compete using different devices.
- Build platforms with the flexibility to accommodate broader needs.
- Develop structured user surveys that address the unique elements of usability of the device and its features. Open-ended questions and qualitative data are helpful in understanding the user experience. Allow for free text responses.
- Get user feedback on the process of fabricating and fitting the devices.
- Look for user feedback on devices in the context of the activities of daily living.
- Use virtual reality environments to test different aspects of prosthetic use and control before implementing the physical device.
- Make the iterative development process more efficient and inclusive.
- Discuss how researchers can assess technology use satisfaction and get feedback from individuals who cannot respond to surveys (e.g., infants and toddlers).
- Find out how people prioritize different needs and what external constraints make those decisions for them.

Developing Translatable Solutions

- Stakeholder engagement in all phases of development and testing can, in theory, facilitate translation.
- Reimbursement is a major barrier that limits uptake. Market size makes it difficult to engage industry partners, and the reimbursement model is too unclear.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

- Having multidisciplinary research teams, including people who understand insurance reimbursement, clinicians who treat patients, and patients and their families, is important to ensure translational success.
- Mobile technology allows for automatic collection of usage data, and some digital therapeutic reimbursement plans offer refunds if the patients do not use the app much.

Stakeholder Engagement and Multidisciplinary Research Teams

Barriers

- Some funding mechanisms do not allow consumers to participate as paid team members or consultants, while others require it.
- The many requirements lead to inequities in where and by whom rehabilitation technology development is done.
- Some populations are very resistant to participating in research because of deep-seated, historical views on human research.

Potential Solutions

- Putting numbers in recruitment tables does not result in engagement of diverse populations. A more concerted effort by individuals and agencies is required.
- Diversity and inclusion need to be expanded at all levels for technology development research to be truly impactful.
- Meeting people where they are—for example, at churches and community centers, not just at the medical center—is a huge step.
- Getting enough participants overall so that the research can look at underserved groups is a barrier that might be overcome with greater data sharing.
- It is not about incentives. It is about culture and message.
- Consumer advocates also act as ambassadors.
- Making data collection more accessible to underserved groups. Take data collection to the participants—for example, through telemedicine and wearables.
- Some NIH Clinical and Translational Science Awards programs have a community recruitment core that can connect researchers with local communities.
- Hire staff who speak languages common in the community or have similar cultural backgrounds.
- Pair with support groups and services that engage the community.

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Theme D: Research Design and Methodology (October 15)

Key Points of Discussion

- Rehabilitation research is not reaching clinical practice to the same extent as other fields of science, likely because small sample sizes, exclusion criteria, and narrow focus on a single therapeutic intervention does not reflect what clinicians do.
- Consider developing review mechanisms dedicated to pragmatic research and implementation science.
- For adaptive trial designs in rehabilitation research, would it be possible to use a synthetic control arm for intervention studies, as used in some cancer trials?
- Rehabilitation research must convince insurers that interventions are not experimental and should be covered. Getting insurers (including the Centers for Medicare & Medicaid Services) on board is key to increasing sample size for pragmatic research studies and facilitating integration of interventions into the real world.
- What are the challenges or potential threats to internal validity with pragmatic trials, and how have researchers overcome them?
- Creating a culture of learning and breaking down barriers between clinical and research missions can be a strong foundation for pragmatic trials with high-quality data.
- Mixed-model design and large sample size seem to be the way forward.
- Mixed-method research design:
 - Could facilitate implementation
 - Contributes to greater depth and breadth of understanding
 - Provides valuable insights from engaged stakeholders
 - Identifies barriers and facilitators of delivering a novel intervention, something that is particularly important for larger-scale implementation
 - Can assist in patient-reported outcomes and adherence to treatment
 - Faces obstacles, such as problems with implementation and adherence, but trial designs, data collection, data standardization, and other advances reduce the impact of those obstacles

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Theme E: Translational Science (October 15)

Research on Multimodal Interventions

Pros

- Necessary to maximize functional gains in neurorehabilitation populations
- Great method if suited accordingly to the person's abilities, background, health status, and living arrangements
- Can increase engagement in, adherence to, and enjoyment of the intervention if stimulating components (e.g., music, gardening, pet therapy) are integrated
- Effective examples in nutrition science and cancer research

Cons

- Pushes against the reductionist model favored by NIH
- Difficult to isolate key ingredients without large sample sizes and multiple treatment groups (control arms may be useful to assess the effects of individual treatments alone)
- Potential for interventions not to have an additive effect
- Should the individual select the intervention or is a series of diagnostic tests needed to determine what would be best?
- Do you need to know the mechanism(s) of action to do a good multimodal trial?
- Challenging to conduct within a 2-year project timeline

Considerations

- Convene a conference to explore multimodal research (include discussions of existing tools like NICHD's Data and Specimen Hub to facilitate data sharing).
- Consider adaptive experimental designs for pursuing multimodal studies—not just for dosing but also for algorithmic addition of additional intervention components based on assessment of ongoing performance or outcome measures.
- Adherence is a big issue in multimodal treatments. The component to which participants were most likely to adhere was uniquely related to change in outcomes.

Topics to Consider

- Biomarkers for rehabilitation research (consider supplements to add biomarker research into existing studies)
- Role of epigenetics in understanding responders and nonresponders

Research Mechanisms and Approaches

- New funding mechanism (e.g., U, PPG) for truly innovative, cutting-edge ideas, encouraging cross-disciplinary and multisite collaboration
- Increased data collection and data sharing across rehabilitation research

Rehabilitation Research 2020: Envisioning a Functional Future

October 15–16, 2020

Theme F: Building Research Capacity and Infrastructure (October 16)

Topics to Consider

- Barriers include the lack of experienced mentors and champions who can guide those new to research and the isolation between clinicians and clinician scientists.
- Improve the validity of rehabilitation research, taking family and environmental support and barriers into account.
- Increase support for those in the rehabilitation field to conduct research:
 - Establish a mid-career development award for training in a complementary area.
 - Provide support for mid-level clinicians to get involved in research.
 - Create links to career mentors who can help with writing research grant applications and navigating the peer review system.
 - Target funding to the issues and questions important to clinicians and their health systems (which also facilitates optimization of solutions and translation of research).
 - Create “fellowships” for full-time faculty to conduct research with a mentor while retaining academic appointments at a home institution.
 - Offer clinicians continuing education credit for research involvement.
- Provide education and support to those in the early career stages:
 - Engage professional students to participate as research partners as a way to help change practice.
 - Provide more funding for programs for rehabilitation researchers to bridge the gap between postdoctoral and independent investigator status.
 - Fund more education research to help get future partners in the clinic.
 - Create awards that require a team science approach.
 - Engage and train clinicians who want to get involved in research but lack training and do not have doctoral degrees.
 - Create dual-degree programs to support rehabilitation clinician-scientists.
 - Leverage loan repayment programs as an incentive to bring professionals into research careers.