



Eunice Kennedy Shriver National Institute
of Child Health and Human Development

Rehabilitation Research Resource to Enhance Clinical Trials Workshop: The Future of Medical Rehabilitation Clinical Trials

National Center for Medical Rehabilitation Research (NCMRR)
6710 Rockledge Drive, Bethesda, Maryland
September 29–30, 2016

Day 1: Thursday, September 29, 2016

Welcome

Alison Cernich, Ph.D., Director, National Center for Medical Rehabilitation Research (NCMRR), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

Marcas Bamman, Ph.D., University of Alabama at Birmingham (UAB); Director, Rehabilitation Research Resource to Enhance Clinical Trials (REACT)

Dr. Cernich explained that NICHD is committed to advancing the science that will have an impact on the lives of people with disabilities. Clinical trials are an important part of this agenda, and NCMRR needs help from scientists like those at this workshop to address the challenges of rehabilitation clinical trials.

REACT¹, funded by NICHD, provides knowledge, skills, and tools to catalyze high-impact, interdisciplinary clinical trials on rehabilitation. Dr. Cernich urged workshop participants and their trainees to take advantage of the REACT resources. Dr. Bamman added that the REACT Center offers four \$40,000 pilot feasibility grants once a year.

This meeting was made possible by the generous donation of a private individual who wanted to advance research in rehabilitation science, especially illnesses that cause death or disability at a high rate in the U.S. population. Drs. Cernich and Bamman thanked the meeting's sponsor and organizers. This meeting will result in a white paper on the future of medical rehabilitation clinical trials.

¹ <https://react.center/>

Design Considerations/Stages of Development

Intention-to-Treat and Per-Protocol Analyses

Gary Cutter, Ph.D., UAB

Three principles of intent-to-treat (ITT) analyses are:

1. Keep participants in the intervention groups to which they were randomized, regardless of the intervention they actually received.
2. Measure outcome data on all participants.
3. Include all randomized participants in the analysis.

The first principle is easy to apply, but the second one is often beyond the investigator's control because study participants might withdraw, drop out, or miss an assessment visit. Principle 3 is then even more problematic, because it can be applied when all participants provide all required data, or when the investigator makes assumptions about the missing data. Imputation of data should be pre-specified to reduce the potential for bias.

The alternative to ITT is the per-protocol analysis, which, like ITT, lacks a consistent definition. Per-protocol analyses can assess the treatment received, everyone who adhered fully to the visit schedule, or everyone who adhered fully to the visit schedule and complied with the treatment recommendations.

To illustrate the challenges of ITT analyses, Dr. Cutter proposed a hypothetical study to test whether a new treatment works. "Works" might mean that people have better outcomes if (1) they use the new treatment instead of the old one or (2) if they *try* to use the new treatment instead of the old one. For definition 1 (the one that most people assume is being assessed), a per protocol analysis can be used. Definition 2 offers the chance to use the treatment and is thus best assessed with an ITT analysis. The ITT can address confounding well, but crossovers from the "try to use" the new treatment imply that the correct effect is not estimated. In contrast, a per-protocol analysis estimates the correct effect, but the difference could be confounded. ITT analyses accept the certainty that the investigator is estimating the wrong effect against the possibility that confounding could play a role in the outcome. Definition 2 also raises other problems: most people *misunderstand* what the trial is assessing, and ITT analyses do not address this question. This approach assumes that people assigned to take a treatment in a trial act like people with prescriptions for the treatment in the "real world."

Multimodal Interventions and Alternatives to Control Groups

Edelle Field-Fote, Ph.D., PT, FAPTA, Crawford Research Institute, Shepherd Center

Dr. Field-Fote recommended assessing multimodal interventions in clinical trials when 1.) the effects of each intervention in isolation have been characterized in the study population; 2.) there is reason to believe that the effects of the treatments will be cumulative; and 3.) there is no evidence of a negative interaction between the interventions.

Claiming to "do nothing" as a control group is not acceptable or accurate: the social interactions involved in coming to the clinic and interacting with the staff can influence behaviors, attitudes,

perceptions, and outcomes. Control group participants' expectations can influence outcomes (e.g., through the placebo, Hawthorne, or Pygmalion effects).

Factors that can influence trial outcomes include whether each intervention group participant attended all sessions, was actively engaged, developed the desired skill, and used or practiced the new skill outside the training sessions (and if so, how much). The possibility that the control group learned what the experimental group was doing and practiced it can affect outcomes.

Approaches to reduce these influences include the following:

- **Delayed-intervention designs:** All participants enter the study at the same time, but half of the participants receive the active intervention immediately and half receive it later. This design is only suitable for non-progressive disorders.
- **Crossover designs:** All participants receive the treatment, but the order of the sham intervention and the active intervention is randomized. This design allows within-subject comparisons and eliminates some problems associated with interpersonal variability. It is appropriate for interventions aimed at controlling symptoms, but not for treatments to resolve a condition.
- **Run-in (or wash-in) designs:** Everyone is observed before receiving the intervention, and all participants receive the same initial trial. The run-in period can include a placebo or an active treatment. This design is appropriate for assessing stability at baseline, identifying placebo responders, or seeing trends in response to run-in active interventions.
- **N-of-1 randomized designs:** Observations are repeated across time. This design is suitable for health conditions that are chronic and stable, interventions with a rapid effect, and measurable and clinically relevant effects.

Discussion

Studies of a behavioral intervention often have negative results, so investigators try multimodal interventions in an effort to produce a small change. The challenge is that if the multimodal intervention has an effect, it is difficult to determine what, exactly, caused the effect. Also, funders might only support studies of combinations of therapies, but not of combinations in addition to studies of each intervention alone.

Longitudinal descriptive studies show that the condition of patients with traumatic brain injury (TBI) does not necessarily get better over time. However, in trials, *both* treatment and placebo groups sometimes do better over time. If empathy and social support are part of the active ingredient mix, the control condition might not be correctly configured. Comparison groups in these studies might need to receive *no treatment* to ensure that outcomes are due to the proposed active ingredient.

Short, unblinded trials that assess subjective responses have a high likelihood of identifying differences between groups. These trials rarely follow patients long enough to show whether the effect is real (i.e., not a placebo, Hawthorne, or Pygmalion effect). Such trials should be blinded or include a second, objective outcome. The level of confidence in the study results should be dictated by the design, research question, and patient biases.

The trial design and selection of a control group depend on the phase of the clinical trial. It is important to identify whether the active ingredient(s) that the investigators believe cause the effect actually have that effect before moving to an expensive, advanced-phase trial. Investigators need to recognize that the total dose of an intervention that patients receive in a trial couldn't be larger than the doses provided in the clinic—for example, if patients increase their activity level at home, total exercise will be larger than the clinic (test) dose.

It is critical to analyze everyone who enrolls in the trial. Statistical methods cannot account for missing data in ITT analyses, or show that results reflect a truly unbiased estimate of the effect. The solution is to use a design that *minimizes or eliminates* missing data. Statisticians assume that dropouts occur randomly, but this distribution may not be the case.

If less than 10 percent of the data are missing, missing data are unlikely to matter. However, if more than 10 percent of data are missing, it is important to look at other issues—such as what caused so many people to drop out? If several approaches to address the missing data produce the same answer, preliminary studies can help build efficacy studies that accommodate realistic attrition rates.

How Much Data Are Enough?

Gary Cutter, Ph.D.

Pilot data are valuable to assess a large study's feasibility, provide evidence that the hypothesis is correct, support sample size estimates for future definitive studies, and test recruitment and retention strategies. However, pilot studies can lead to course changes that can delay the design of a definitive study.

Blinding/masking is designed to ensure objectivity. Our most common example is blinding the assignment to a placebo pill vs an active-ingredient pill. However, blinding can be difficult for interventions that are not pills. When double blinding is not possible, masked observers can be used. In unblinded studies, regression to the mean often impersonates a treatment effect.

Bayesian designs are a philosophy, not a statistical design. They are best for phase II studies when estimation is warranted. Other modern designs include:

- **Targeted (enrichment) designs:** Use a predictive biomarker to choose the target population for treatment. Advantages include the need for fewer randomized patients; for instance, when fewer than half of subjects have the biomarker and treatment has little benefit in those without the biomarker.
- **Adaptive designs:** Conducted in incremental stages and based on pre-established rules for allocation, sampling, stopping, or decisions about next steps, allows a change to the design. . Interim monitoring is used to stop enrollment as soon as possible for safety, efficacy, or futility or to increase enrollment.
- **Sequential, multiple assignment, randomized trial (SMART) designs:** Make critical decisions and randomize participants at each stage in multistage trials. SMART designs are used to construct adaptive treatment designs and to examine therapeutic strategies.

Multiple endpoints can be handled through multiple statistical tests on a single dataset. In hierarchical/rank-order testing, each endpoint is only tested if all previous endpoints have statistical significance. The other option is to treat all endpoints equally but require a smaller p-value to claim significance.

Discussion

Peer reviewers have approved clinical trials with adaptive and other new designs. For example, the Patient-Centered Outcomes Research Institute (PCORI) funds several pragmatic studies that use adaptive designs.

In rehabilitation research, the question of whether to move forward using pilot data is not whether the effect was statistically significant (because effect sizes are often very large in small pilot studies) but, rather, the magnitude of the change compared to best medical management or routine care. The distinction here is between statistically significant and clinically meaningful changes.

Evolving Topics and Considerations in Clinical Trials

Ken Saag, M.D., M.Sc., UAB

Stephanie DeLuca, Ph.D., Virginia Tech Carilion Research Institute

Types of trials used in the translation continuum include the following:

- **Efficacy trials:** Indicate whether an intervention is effective in ideal circumstances, use selected populations, tightly controlled assessments, and strict protocols. They have high internal validity, but may have poor generalizability.
- **Effectiveness trials:** Assess what happens in real-world circumstances and therefore have low internal validity, but high generalizability.
- **Pragmatic clinical trials:** Measure real-world effectiveness of interventions in large samples, so their results are generalizable; have minimal inclusion and exclusion criteria; test simple interventions to minimize risk; measure objective, patient-centered outcomes; compare the practical value of new treatments to that of existing treatments.

The NIH approach to enhance rigor, reproducibility, and transparency is changing application instructions and review criteria. Reviewers now evaluate scientific premise as part of the significance criterion and evaluate scientific rigor and relevant biological variables as part of the approach criterion. NIH's new policy on use of a single institutional review board (IRB) for multisite studies will go into effect in May 2017. A central IRB may provide reviews for sites participating in more than one multisite study, often as part of a consortium or network.

Treatment fidelity is the extent to which the treatment delivered to a patient matches the treatment specifications. Many medical rehabilitation interventions are not sufficiently specified or described in manuals, which prevents rigorous fidelity measurement. Medical rehabilitation trials rarely monitor treatment fidelity, but doing so is key for implementation science. This

discipline investigates facilitators and obstacles to effective implementation of research results and tests new approaches to improve health care delivery and maximize intervention effects.

Comparative effectiveness trials provide a rigorous test of the relative effectiveness of variations in treatments for a given type of rehabilitation. However, any five articles on a given rehabilitation intervention are likely to describe five variations of the intervention. The field needs to do a better job of comparing treatments—or their variations—with one another through traditional randomized controlled trials (RCTs) or comparative effectiveness trials.

Discussion

A major advance from the mental health field was creation of protocols for interventions, checking their fidelity, and monitoring those who deliver them to ensure that they provide the interventions they say they provide. Rehabilitation protocols lack this consistency and consequently can be deemed not evidence-based.

Constraint-induced movement therapy (CIMT) is the rehabilitation intervention backed by the most research, but it has many different protocols for implementation. As a result, many interventions called CIMT are delivered that are not evidence-based. Furthermore, rehabilitation medicine practitioners tend to mix together components of different evidence-based protocols instead of following an evidence-based protocol with fidelity. Because patients who need rehabilitation interventions tend to have multiple impairments, providers often mix components of an evidence-based protocol with components of other protocols to treat comorbidities.

The challenge is how to turn routine clinical encounters that involve interventions that are not evidence-based into research encounters. This is a “moral imperative” because this research has value to society. The widespread availability of electronic health records (EHRs) could help make such studies possible.

Clinical trials that use a “usual care” control group must determine typical care, which is difficult when each patient receives different interventions. One solution is to give the control group “usual care” but acknowledging that this care can vary.

Engaging community practitioners in science has been difficult, which is one reason why evidence-based results are not translated to the community. Several disciplines of rehabilitation care providers must be engaged in the science.

Researchers are sometimes reluctant to use a control group that receives no intervention in rehabilitation studies because participants need services. However, funders/peer reviewers often require a control group to strengthen a design. One solution, as discussed earlier, is to delay the intervention in part of the sample.

When classifying active ingredients of rehabilitation, it is necessary to distinguish between ingredients that generate the *treatment effect* and those that generate the *motivation to do the activity* if the intervention involves one. If the ingredients are weak, the treatment should be tweaked, but approaches to improve compliance are different. In addition to measuring patient adherence, researchers must measure clinician fidelity to prevent drift.

All of the data that researchers collect in clinical trials, including treatment fidelity data, should be entered into a database, analyzed, and published.

Critical Staff

Carla Perna, UAB

Carolee Winstein, Ph.D., University of Southern California

The **research coordinator** is critical to clinical trial success. Although this position must sometimes be filled by a nurse, this is not always the case. The research coordinator supports, facilitates, and coordinates daily clinical trial activities under the direction of the principal investigator (PI). The research coordinator ensures compliance with good clinical practice, local and state laws, and NIH or FDA requirements for clinical trials. The research coordinator, who needs training and often certification, also provides training to other trial staff on changes in policies and regulations.

The **outcome assessor** administers outcome assessments according to the study protocol and Manual of Operations, and demonstrates that he or she is doing so correctly. This individual should receive pre-enrollment training, which must be included in the study budget.

All **interventionists** must be well trained and retrained regularly to ensure that their performance meets pre-specified criteria for treatment fidelity. Interventionists in multisite trials should have regular meetings to deal with concerns and share insights across sites. Fidelity checks should be included in exit interviews with patients. Special training and blinding procedures are necessary if clinic personnel are to assess outcome. For efficacy studies, research staff deliver the intervention to show whether the intervention has an effect under optimal, controlled conditions with expert, trained, and standardized clinicians. In effectiveness studies, clinical staff should administer the intervention to show whether the intervention works in real-world clinical environments.

Discussion

Investigators submitting applications to NIH often underestimate their staffing needs, or their administrative structure does not cover all of the activities they propose. Budgeting problems are difficult to address after peer review, and can jeopardize decisions to move forward.

Multisite trials might have a lead research coordinator who oversees the site coordinators. All site coordinators must use standardized forms and processes, and they should have regular conference calls to prevent drift. Alternatively, a committee of site coordinators can make consensus-based decisions about standardization. Steering committee meetings should include breakout sessions for site coordinators. Coordinators contribute to the science of the trial, and they should be encouraged to present at national conferences and prepare publications.

Investigators who use research staff in the pilot study often wonder why the intervention did not work when they used clinical staff in the larger trial.

Recruitment and Retention

Jennifer Stevens-Lapsley, Ph.D., PT, University of Colorado
Mona Fouad, M.D., M.P.H., UAB

Some barriers to recruitment are related to the targeted community, including their health beliefs and life priorities, socioeconomic status, and level of fear or mistrust of research. Most clinical trial participants have a positive experience; however, ninety percent of trial participants report that they would like to know the results of the trial, but only 7 percent receive that information. This lack of communication reflects poorly on the research enterprise, and may persuade patients not to enroll in another clinical trial or to discourage others.

Recruitment barriers can also be related to health care providers who may serve as clinical sites in a study. Providers may fear loss of control over what happens to their patients if they participate in a clinical trial; the legal liability of referring patients to a study that might harm them; the uncertainty about how to explain a clinical trial to a patient; or a lack of information about patient progress during a trial.

Other barriers to recruitment and retention relate to study design: complex consent forms, patient concerns about being in a control group, and the time and complexity required for participation. The costs of rehabilitation in RCTs may limit sample size, and/or require strict inclusion and exclusion criteria to increase control. Investigators must be aware that more homogeneous samples can lead to less generalizable results

Recruitment tips for study staff in rehabilitation clinical trials include:

- Remind site staff regularly about recruitment/retention goals
- Eliminate the need for your referral sources to provide time-consuming explanations to patients
- Send providers updates on their progress, and progress of the trial
- Engage colleagues as coinvestigators
- Spend time in providers' offices/at sites to understand the workflow
- Send regular thank-you emails to providers/sites
- Engage champions in each office or site that sees patients or enters data
- Hire graphic designers to create professional-looking advertisements
- Ask patients and community partners for suggestions

Investigators often focus on recruitment, but have few plans to address dropout. Investigators can prevent some loss-to-follow up by using exclusion criteria, but maintaining participation during the trial requires resources (e.g., non-monetary incentives, assistance with transportation or child care). Staff must attempt to recover patients who miss appointments through case management and an open door policy to encourage return to the study.

Dr. Fouad has used clinical trial navigators to help under-resourced patients complete specific trials. For example, when the navigators educated patients in oncology clinics about clinical trials, clinic personnel began referring minority patients to the patient navigators for information. The refusal rate dropped and the minority enrollment rate increased.

Discussion

Many universities and hospitals use their patient databases to identify patients to recruit to clinical trials. This practice raises ethical questions. Recruitment should be approached as a science that has a design, a methodology, regulations, and ethical principles that it must follow. Retention/recruitment efforts should not introduce bias into the study; this concern is reduced when retention staff are separate from staff responsible for delivering study treatment or assessing outcome.

An alternative to examining barriers to recruitment is to identify facilitators, such as an altruistic desire to help other patients through clinical trial participation. This area is ripe for qualitative research that can expand the understanding of how to engage patient populations.

The rehabilitation culture itself is a recruitment barrier, because it emphasizes “off-label” uses of interventions. The need to test an intervention may not be obvious, when practitioners routinely vary their approaches for each patient.

Data Entry and Management

Darcy Reisman, Ph.D., PT, University of Delaware
Anne Lindblad, Ph.D., EMMES Corporation

The first step in data quality assurance is to define standards for the intervention and outcome measures in an operations or procedures manual to ensure that all study personnel can implement the intervention and conduct assessments in the same way. A data management handbook can provide instructions for completing forms, submitting data, and monitoring data quality.

Training ensures that study personnel understand what they are supposed to do. A training checklist can help ensure that all personnel have received the necessary instruction. Evaluating compliance with procedures and regulations by all study centers is necessary. Datasets should document who enters each data element and details on every data point (Data Dictionary). Even when a trial is not aiming at FDA approval, making sure that all data are correct is good practice. Data sharing requirements from NIH reinforce this point.

Electronic case report forms help keep the data “source” as close to the database as possible. Best-in-class data systems can help with clinical trial management. At one institution, clinicians complete forms on an iPad that they carry with them. They cannot close out a record if a critical item is missing or if an entry is out of range. These forms collect outcomes and treatment fidelity data.

The information in Electronic Health Records (EHR) might not be consistent with what research requires. For example, the cause of death in an EHR might be listed as heart failure in a patient with cancer. It is important, however, for staff to avoid wasting resources by entering the same data into a research database and an EHR.

Many groups monitor clinical trials, including the FDA, IRBs, NIH, PIs, lawyers, and the public. This scrutiny ensures that reported trial data are accurate and complete and that they contribute to improving patient care. Monitoring can be on site, central, or off site. Site visits are expensive but can be used to qualify and initiate sites, audit data, and close out sites. Items to inspect include equipment, documentation, specimen storage, secured areas, and mechanisms for processing and shipping specimens. Inspectors must also ensure that staff have the appropriate training and certification, and they must check adverse event documentation and reporting.

Investigators must plan how they will close out their trial before starting the study. For example, they need to determine what to do with records and how to redact personal health information in shared data.

Discussion

The ability to exchange data electronically with others outside the study has not kept pace with technological advances. Sharing data is a goal for NIH-funded studies, and many institutes have disease or discipline specific repositories. Questions to consider include:

- Where should investigators house data on community members who are not affiliated with the academic medical center?
- What security rules apply to these data?
- How can investigators send messages or emails to participants or “next-of-kin” without compromising data security?

Different sites have different policies about electronic data capture for research; an example is REDCap (<http://ctsicn.org/tools-and-resources/redcap>).

Each institution sponsoring research should provide guidance for its investigators, and these details should be worked out before designing a study or submitting a grant. A central electronic system will help standardize these processes, and researchers need to ask their IRBs to agree to standardized procedures.

Computer data entry systems can use range checks to flag data entries that might be incorrect. The closer to the time of data entry that these checks happen, the greater is the chance that the entered data will be accurate. Additional sophisticated algorithms to check data accuracy beyond range checks are available. Deviations identified through a treatment fidelity checklist can be approved if the person who entered the data provides a rationale.

Making clinical trial data public is an important goal, and ensuring that data are complete and accurate requires time, resources, and planning. Ideally, all clinical trials in rehabilitation would use the same common data elements (CDE) in case report forms. At NIH, several CDE repositories are available, including <https://www.commondataelements.ninds.nih.gov> and <https://www.phenxtoolkit.org/>. Increasing standardization helps the field move forward.

Data and Safety Monitoring (DSM)

Catherine Lang, Ph.D., Washington University
Anne Lindblad, Ph.D., EMMES Corporation

The purpose of DSM is to review ethical issues for trial participants and patients in general, monitor the trial's safety on an ongoing basis, and determine whether to stop the trial early for benefit or futility based on interim results. NIH usually requires a data and safety monitoring board (DSMB) for multisite, phase III trials, and a DSMB might be appropriate for high-risk phase I or II trials. Smaller, lower risk studies need at least a predefined, written safety plan.

NIH requires the DSM plan to specify the information to be monitored, frequency of monitoring, interim analysis plans, stopping rules, and process for monitoring and reporting adverse events and unanticipated problems. The plan must also identify who is responsible for monitoring and advising on the trial. This entity can be the PI for low-risk, non-blinded studies; an independent safety monitor or designated medical monitor; an independent monitoring committee; or a DSMB. The plan must also describe the safety responsibilities of the investigator, sponsor, medical and safety monitor, and pharmacovigilance providers.

NIH requires a DSM plan in the grant application, and expects reviewers to comment on it. The trial's manual of procedures can include sections on safety, define an adverse event (AE) or serious adverse event (SAE), and specify what to do when an adverse event occurs. It is important to identify potential adverse events in advance and list these events in forms to ensure that staff monitor them at appropriate times.

The DSMB advises the sponsor, which can choose whether to take its advice, and ensures that clinical trials proceed ethically and produce valid and credible results. The board, which is independent of the sponsor and investigators, reviews accumulating data for strong evidence of treatment harm or benefit (efficacy and safety) and of inefficacy and futility. Each DSMB should have a charter describing its roles and responsibilities, meeting logistics, conditions of appointment, data management and security responsibilities, study review criteria, document management procedures, and reporting requirements.

Questions often arise about whether the DSMB should review unmasked data, whether the study chair should be part of the DSMB, and whether the sponsor should attend closed sessions. Other areas of debate are the distinction between stopping rules and guidance, and the roles of the DSMB versus those of the IRB. Investigators who propose studies that require a DSMB must coordinate with their universities and funding agencies to ensure that systems are in place to support this considerable effort.

Discussion

Dr. Lindblad supported a "reasonable person's approach" to deciding how independent the DSMB members must be from the investigator. It is important to consider the expertise that each member brings to the DSMB; however, a person who has authority over the PI or who is under the PI's authority does not "smell right." It can be difficult to find DSMB members with

appropriate expertise who have no links to the investigators, so full disclosure by DSMB members is critical.

NICHD has DSMB guidelines, and allows investigators funded under many grant mechanisms to set up their own DSMB. Some studies can use a standing DSMB, such as one created for a Clinical and Translational Science Award, to assure NIH that the committee's composition is appropriate.

The safety culture is different for non-pharmacologic and pharmacologic clinical trials. Investigators typically view non-pharmacologic trials as safe, and they monitor these trials for obvious/expected adverse events, such as falls. In contrast, pharmacologic trials are monitored for everything, although most adverse events tend to be classified as probably unrelated to the study drug. The list of potential events to monitor in rehabilitation trials could be infinite; each trial must assess what they will report as AE/SAE's

A suggestion was to create a comprehensive list of events to monitor and use open-ended questions to gather information about events not listed. At the same time, studies need to guard against collecting too much data, which could actually mask some small events. Studies could collect data on all hospitalizations and on pain levels before and after every session to identify the types of events that are important to patients. However, this approach would not identify the risks of a cognitive intervention, such as inadvertently making another cognitive skill worse or affecting another aspect of cognition.

Expected adverse events must be documented in annual reports but need not be reported to the IRB immediately. IRBs want to learn about unanticipated adverse events, including those that are more common or more severe than expected. Investigators must be familiar with IRB policies that will affect their trial, and have the processes well in hand. NIH policy on IRB review of multi-site studies must be considered.

At some institutions, any clinical trial of a medical device, even a phase I trial, must have a DSMB. Likewise, Behavioral phase I/II trials at a single site that are low risk need a safety monitoring plan and should have a safety monitor, who could be the PI (depending on the level of risk). Whether a multisite phase I/II trial needs a DSMB depends on the amount of risk. Phase III trials should definitely have a DSMB.

NIH institutes and centers have different policies on which trials need a DSMB. All clinical trial applications to NIH must include a DSM plan. At several ICs for Phase III studies, NIH will be responsible for appointing a DSMB, reports to NIH, not the investigators. As with any aspect of requesting NIH support of a clinical trial, investigators are strongly advised to contact program staff early in their planning process.

Outcome Measures for Different Phases of Translation

John Whyte, M.D., Ph.D., Moss Rehabilitation Research Institute
Daniel Corcos, Ph.D., Northwestern University

The translation process in rehabilitation does not always follow the phase I, II, and III sequence, and the methods associated with each phase in pharmaceutical trials do not necessarily apply to rehabilitation trials. For example, an early proof-of-concept rehabilitation trial of TBI might need an untreated control group because of patient variability and potential for natural recovery. Instead, the translational process in rehabilitation research may begin with the traditional generation of ideas based on studies in tissue, animal models, and other patient populations, but also may include clinical observations and natural history studies. The next steps are early human testing for safety and proof of principle, large-scale efficacy testing with many iterations, and then effectiveness assessment.

Two classes of theory that are relevant to rehabilitation research translation are:

- **Treatment theory:** Used to determine a therapy's active ingredients and mechanisms of action.
- **Enablement theory:** Used to make predictions about the ultimate functional impact of the treatment-induced changes.

Knowing a treatment's mechanism of action lets the investigator choose an outcome measure that is linked to the entity that the mechanism of action will affect most directly. In many rehabilitation treatments, the mechanism of action is not precisely known. As a result, some early studies might need to use multiple outcome measures to determine the changes produced by the active ingredients of treatment.

Stroke and other forms of brain injury usually produce many physical and cognitive impairments, and the clinical goal is to restore functioning in important activities that are restricted by complex combinations of the impairments. The link between treatment of the impairment and larger gains is usually tenuous. For example, the prediction that improving working memory will enhance the patient's ability to do his or her professional job will be shaky. Enablement theory addresses the causal relationships among variables at different levels within the International Classification of Functioning, Disability, and Health.

Each IC at NIH has requirements governing submission of clinical trials, regardless of the "phase" of the research. For example, investigator-initiated applications that include clinical trials for funding by the National Institute of Neurological Disorders and Stroke (NINDS) must be submitted in response to one of two funding opportunity announcements: NINDS Exploratory Clinical Trials (PAR-13-281 for R01 grants) or NINDS Phase III Investigator-Initiated Efficacy Clinical Trials (PAR-13-278 for U01 grants). Exploratory studies funded by this institute cannot be scaled-down versions of an efficacy study, but they should explore key details that could derail a phase III trial. The investigators need clear go/no go decision rules for a phase III trial and some exploration of such a trial's design.

Discussion

Outcome measures of life participation are virtually nonexistent for stroke, and investigators tend to assume that measuring level of activity is a proxy for life participation. If a phase III clinical trial shows that an intervention changes activity levels without translation to life participation, which is where most investigators want to see changes, is the money well invested? Some TBI interventions can affect life participation, such as supported work or community reentry programs. It is difficult to untangle the heterogeneous connections between various rehabilitation interventions and these outcomes.

A challenge in rehabilitation is that the failure to change critical behaviors in patients' daily lives will not lead to long-term improvement. In addition, changes in life participation might take much longer than changes in activity levels. In one upper-extremity study, patients did not appear to improve during the study; but several years later, they reported that their lives had changed.

Technology is useful for measuring changes in life participation. For example, it is possible to identify a patient's location through GPS tracking and find out what the patient did in each location through interviews. However, life participation is multimodal, and what is meaningful varies. Participation at a different level might not be related to the patient's disability. Investigators should measure changes in both activity and participation levels in a standardized way. Many measures assess capacity, or what people *can* do. But the measure of real interest is what the participants actually do, which is performance. Research is needed to understand the distinction between performance and capacity.

Investigators must define and refine treatments based on active ingredients. First, develop a theoretical model about the likely effects of the active ingredients and then spend sufficient time at an early stage of development on exploration and learning.

Models beyond rehabilitation are relevant, such as those from behavioral economics that address social and behavioral context. Behavior and adherence are critical to rehabilitation, and experts in this field should be brought into rehabilitation trials. It might be possible to learn as much from practice-based evidence as from evidence-based practice. The context within which patients are acting is important. Behavioral medicine experts who try to understand or change behavior use momentary ecological assessments. Monitoring devices could collect both qualitative and quantitative data about the social context and its influence on patient attempts to implement an intervention.

Studies have identified many factors that moderate the influence of a person's capacity on his or her performance. This information could be used to identify new targets for interventions.

Follow-up: Sustaining Treatment Effects over Time

Kathryn H. Schmitz, Ph.D., M.P.H., Pennsylvania State University
Robert W. Motl, Ph.D., UAB

Producing a durable effect requires continued participant. Participants need a resource (such as a tool or education) that helps them sustain change over the long term.

The use of theory informs the search for antecedents and the development of interventions to change health behaviors. Theory can help identify variables to target for behavior change, strategies for manipulating variables, and how to implement such strategies. For example, social cognitive theory posits that people learn by observing others and imitating their behaviors. When this process is reinforced, the behavior change becomes durable. Dr. Motl used this theory to develop behavioral platforms, such as an internet-delivered platform for changing free-living physical activity behavior in people with multiple sclerosis. This platform addresses all social cognitive theory components, including self-efficacy, social interactions, self-monitoring, and goal setting. An RCT found a large, statistically significant increase in physical activity in the intervention group compared with the wait-list control group.

Subsequently, the investigators changed the intervention based on feedback. They replaced the chat rooms with individual discussions (TeleCoach) to enhance users' understanding of the material. They delivered the intervention for 3 months and then took the website down. The intervention group increased physical activity levels and sustained this increase for 3 months after the intervention ended. An explanation for the durable effects is that the intervention taught participants to self-regulate their behavior and integrate physical activity into their daily lives without support from interventionists.

If an investigator's main goal is to produce sustainable changes, he or she should consider sustainability at all stages of the research. If the main goal is a particular patient outcome, sustainability can be considered at later stages of research. Dr. Motl started his sustainability approach before the feasibility stage by asking people with multiple sclerosis about what they wanted for long-term involvement in exercise. Based on their responses, the investigators created a toolkit with a manualized program for integrating home-based exercise into their lives. The toolkit includes a pedometer, log, and exercise band, and participants receive individualized encouragement through Skype. A phase II trial of this program will determine whether its effects are sustainable.

Sustainable interventions are effective, feasible for therapists to implement, based on a manual, low cost, easy to refer patients to, and implementable at home or in the community. Staff training must be inexpensive and brief, and an infrastructure must be in place to sustain them. These characteristics are not the case for most rehabilitation exercise trials.

Dr. Schmitz has shown that weight training is sustainable at YMCAs for breast cancer survivors with or at risk of lymphedema. These studies showed that weightlifting was safe, reduced by half the number of flare-ups needing therapist treatment, and improved quality of life and bone health. Challenges to sustaining these benefits included the lack of infrastructure to continue the intervention within YMCAs or clinical settings for cancer patients, staff turnover, and lack of

marketing to breast cancer survivors. One year after completing the trial, 20 percent of participants were still going to the YMCA. Reasons for not going included lack of affordability and transportation. Dr. Schmitz and colleagues changed the intervention to give participants the choice of a YMCA membership or using home equipment. The revised intervention could be funded by patient payments, copayments to the physical therapist, or a combination. The intervention maintained its safety and effectiveness after translation to clinical practice.

Discussion

A simple way to assess sustainability is to prospectively determine whether the intervention's effect is sustained 6 to 12 months after an intervention ends. Alternatively, investigators can first implement the intervention in a real-life setting, evaluate its acceptability, and then back up to determine how to make the intervention effective. How long to continue an intervention to achieve sustainability depends on many factors.

Efforts to ensure sustainability, whether through environmental or educational approaches, must begin at the start of the research. For example, Dr. Motl is now discussing with providers how to implement an intervention that he and his colleagues are developing. Part of their discussion is how to keep the intervention in place over the long term.

FDA approval of an intervention does not guarantee clinician acceptance. Investigators must anticipate how to disseminate their intervention while they are planning their clinical trials. One essential approach is to ask clinicians to help design the trial and thereby gain a sense of ownership of the intervention. Investigators must consider these sociological and cultural factors to ensure that an intervention shifts from being commercially available to standard of practice.

Dissemination and implementation science now has theories about the characteristics of organizations and interventionists required to sustain interventions. Infrastructures are being developed to understand why an intervention will or will not be sustained.

The transition from T0 to T4 is circular, not linear, and involves many interactions between stages. The community that will adopt an intervention can include providers, organizations, and users, and the principles of community-based participatory research call for involvement of the community starting in the study design phase.

It is important to take users into account when designing research by determining whether the trial addresses an endpoint of value to potential users (patients or clinicians). The specific users will need education about the importance of the target effect. For example, many breast cancer survivors will only value an exercise program if they understand the activities that it will enable them to do.

Investigators can form networks of patients and physicians that they can quickly survey when questions pertaining to sustainability arise. Patient-powered research networks enroll large numbers of patients and monitor them by telephone.

Although many patients are happy to receive interventions from non-specialists, in some cases patients prefer receiving an intervention from a specialist physician, such as a neurologist,

oncologist, or physiatrist. Patients often obtain care from teams of providers, so they are used to seeing several clinicians. Where an intervention will be used is an important part of its sustainability: will the clinician have the personnel, time or training to properly accomplish the intervention?

Sustainability issues for progressive conditions can be different than for static conditions. Patients with a progressive disease might be more motivated to prevent continued decline, whereas those with an acute episode (e.g., stroke, TBI) might be less interested in exercising to prevent some disease or disability they might or might not develop later.

If cost analysis is part of the research, health economists should be consulted to determine contributors to the cost of the intervention and the cost of the disorder. This information will affect feasibility for adoption. Engaging payers early in the development of clinical trials can enhance their willingness to pay for services or change their payment structure as a result of the trial. Identifying all of the relevant billing codes for an intervention can help evaluate and facilitate third-party coverage.

The social determinants of health can affect the adoption of interventions, and researchers can use EHRs to remind physicians to refer patients to an intervention.

Day 2: Friday, September 30, 2016

Technology

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In the existing health care system, a population that wants good health interacts with systems that deliver health care. This fee-for-service approach is very expensive. In the emerging health care reform landscape, the health care system receives a bundled sum of money to manage a population of beneficiaries for a fixed time period. In this population health world, health care services become the system's expenses. The system becomes motivated to deliver only needed services (including primary and preventive care); it has less appetite for filling expensive acute and post-acute hospital beds or performing costly procedures aimed at non-life threatening outcomes. Technology can facilitate the success of health care systems in this new world by reducing costs, maximizing treatment fidelity, and increasing effectiveness and clinical relevance. The pathway to translation (T1-T4)² often starts with preclinical, basic science. The "valley of death" lies between T2 and T3, where clinical trials are conducted to obtain FDA approval or show efficacy. Advancing medical devices further down the translational continuum requires satisfying FDA requirements. But even if an intervention receives FDA approval, it will not change the world unless the world decides to use it, no matter how much evidence is

² <http://georgetownhowardctsa.org/home/what-are-the-stages-of-translation> is an example of the discussion of stages of translation.

available. Many interventions in rehabilitation are standard-of-care, based on no evidence, and providers do not necessarily accept interventions that are based on evidence.

For rehabilitation trials, technology can be an intervention or it can facilitate performing a clinical trial. Technology can be useful in both efficacy and effectiveness trials. For example, technology can objectively measure various outcomes, such as kinetics and other physiological parameters, in efficacy trials without relying on expensive clinician time. In effectiveness trials, technology can monitor treatment fidelity and adherence. A challenge is measuring outcomes while avoiding the Hawthorne effect.

Technologies can be used in research to develop electronic versions of traditional tools and forms, for automated data collection, and as interventions or adaptive protocols. Data can be collected automatically, without any action by the researchers or participant. Protocols can even change based on real-time evaluations of variables.

The advantages of technology (electronic) over paper forms include better data accuracy, the ability to monitor treatment fidelity automatically and adapt interventions without delays, automatic remote monitoring to ensure compliance, simplified data processing, and easily generated reports. Disadvantages include costs and the need for expertise, equipment, and maintenance. Security is usually addressed by data encryption, but remote data collection can intrude in participants' lives in new ways. Accessibility to the internet, cell phones, equipment is also a concern.

Discussion

High-tech interventions with high-tech outcome measures generate a level of enthusiasm that low-tech approaches do not, even if the results are equivalent or only slightly better. Sometimes the interventions used in rehabilitation are not “bright and shiny,” but that does not mean that they are not effective. The demand from funders for more innovation is driving researchers to push technologies harder and faster than they should. Technology is not always the answer, and health care reform might force payers to recognize that more expensive technologies are not necessarily better.

Some communities still have dial-up internet access only, but access to technology has increased with the widespread use of cell phones, even in low-income communities and developing countries. Older adults, especially those older than 70, are not always comfortable using technology. For example, younger patients love video games to engage their limbic systems as part of an intervention, but older patients do not. Investigators need to address these disparities.

Some individuals, particularly members of underserved communities, do not like being monitored because they view it as intrusive. Approaches are needed to overcome this barrier to developing trust.

Although technology can measure many things, researchers still need to determine which things need to be measured. This work is labor intensive, and unlikely to result in publications, but needs to be done. The validity and reliability of devices needs to be checked. For example, smart

watches and cell phones do not count steps well in people with a slow gait. Technology will advance more rapidly than researchers' ability to validate new devices for each population.

Although many believe that the more data you collect the better, collecting large amounts of data on large groups of patients might not generate a large enough signal to dominate all of the noise. Statisticians are unlikely to be able to use these data to come up with the answers that researchers seek.

Typically, the costs of technology drop over time. But until the sustainability phase of research is reached, the cost-benefit tradeoff cannot be known. Perhaps more passive devices that lead patients through a routine are more sustainable than devices that require more effort to use. Researchers need to make sure that the benefits generated by the technologies are worth the cost, but determining this, especially at an early stage, is not easy.

Using technology to monitor behavior can affect that behavior. Many questions need to be answered before technologies are adopted. In addition, patients should be given a choice about whether to be monitored electronically or to upload their data themselves. Many people enjoy using technology and submitting feedback.

Patient communities can launch studies in large populations and receive answers within weeks. This provides a great opportunity for researchers to obtain answers to questions that are important to daily practice.

Inter-Individual Response Heterogeneity

Marcas Bamman, Ph.D., University of Alabama, Birmingham
Sean Savitz, M.D., University of Texas

When investigators conduct clinical trials of any sort, they want to determine whether changes in the mean were statistically and clinically significant, but this approach misses the extremes. Focusing on the mean ignores the significant proportions of patients who were low responders (or non-responders) and the high responders. This often overlooked variance can reveal important predictors of differential responsiveness, lead to improvements in intervention design, and facilitate development of precision rehabilitation approaches.

The factors that can influence response heterogeneity can be modifiable (e.g., comorbidities, functional capacity, physical activity, sleep) or non-modifiable (e.g., age, gender, race/ethnicity, disease). Sources of response heterogeneity in rehabilitation include the specifics of the condition and, for chronic diseases, disease stage and duration.

K-means cluster analysis can be used to understand response heterogeneity by identifying groups based on one outcome measure and probing all potential sources of their responses. Investigators can control for various factors *a priori*, including comorbidities, physical activity, modality and prescription dose, and adherence/compliance. Cellular and molecular sources and predictors that can then be assessed include baseline tissue transcriptome, gene expression, cell signaling responses, and ability to upregulate cellular protein synthesis by ribosome biogenesis. In one

study, this type of cluster analysis revealed differential transcript profiles associated with resistance training-induced hypertrophy in human skeletal muscle.

In the planning stages, investigators can leverage predicted heterogeneity to substantially increase secondary data yield and to power a clinical trial based on predicted numbers of non-responders, low responders, and extreme responders instead of the mean.

Reviewers and funders need to embrace exploratory aims instead of criticizing applications that include them. When funders cut exploratory aims, investigators might be able to find funding for these components of their study using other resources (including REACT <https://react.center/>). Furthermore, resources need to be shared to maximize the yield from rehabilitation trials. A Research-Match should be established to help investigators find specimens and data from completed studies.

Discussion

The NICHD Data and Specimen Hub <https://dash.nichd.nih.gov/> is a centralized resource where researchers can store and access de-identified data from NICHD-funded research studies for secondary research. Other NIH ICs support repositories for data and specimens.

Too often, the mean results from trials are translated as if they are the “one truth.” Rehabilitation researchers need to continue to be very exploratory. Investigators can first try to produce the main effect in their trial and then identify heterogeneous outcomes. However, if a study has no main effect, exploring heterogeneity is difficult. An alternative is to determine in advance who is likely to respond, choose participants with those characteristics, and then expand the study population more broadly. At earlier phases, when studies have small samples, the ability to find subgroups is limited.

What should investigators do when responses to treatment are multimodal rather than continuous distributions? One option is to change the cut points and remove the modest responders who represent the mean. In a study by Dr. Bamman, a comparison between extreme responders and low responders identified 5,000 differentially expressed genes in baseline muscle. But only 182 genes were differentially expressed when the extreme and modest responders were compared, and only 28 genes were differentially expressed in a comparison of moderate and non-responders. The investigators could then focus on determining what made each group so different.

Dr. Bamman uses assessment of heterogeneity as a probing technique to identify people who need to be treated differently and to understand the reasons that one group did or did not do well. Investigators might revisit their clinical trial datasets to determine predictors of heterogeneous responses.

Statisticians can use many analysis programs to explore heterogeneity, especially for genetics. Existing data are useful for validation to determine whether findings from exploratory studies apply to other databases.

Other disciplines, such as psychology, have explored the environmental, behavioral, and social factors that might contribute to differential responses. Rehabilitation researchers should consult these disciplines to determine how to individualize treatment recommendations and provide guidelines for responders and non-responders in real time.

The techniques that Drs. Bamman and Savitz discussed are not unique to physical interventions. For example, every medication has non-responders and they have been explored well in some cases but not in others. Capitalizing on existing data to make interventions more precise can provide many valuable lessons.

Genomics is not the be-all and end-all of heterogeneity. It accounts for some of the variance and is valuable when it predicts outcomes. Environmental and behavioral factors are also critical, and environmental factors are sometimes primary determinants of heterogeneity. All of the factors need to be explored.

Review of Topics and White Paper Considerations

Participants discussed high-priority topics within each domain of the workshop agenda.

Design Considerations

The first session featured several clinical trials designs, and no single perfect design exists for any study. Investigators must make compromises in the questions they seek to answer, the resources they have to answer these questions, and the designs they can apply to achieve their goals.

Investigators must identify the phase or stage of their research, which can be difficult. Some overarching similarities among different types of research can help reviewers, readers, and investigators convey their research stage. Investigators also need to understand the influence of individual interventions, their potential interactions, and the differences in patient responses when exploring multimodal interventions.

Participants agreed that the white paper need not describe the many design options for clinical trials because this information is available elsewhere. They recommended, instead, providing guidance on how to choose the most suitable design for a given rehabilitation clinical trial. The white paper should also discuss control groups, including use of a group that receives no intervention, especially in the early stages of a study when an intervention's mechanisms are not yet known. Because many patients receive no services after a stroke (for instance), the standard of care might be no treatment.

Providing usual and customary care to the control group also needs guidance because the types of care patients receive varies, although a standard care group could receive the care recommended in clinical guidelines. It will be important to distinguish *usual* from *standard* care because many conditions have no standard care. The paper will need to explain that usual care

varies widely and quantify this variation as well as possible. Studies that include a usual care group are two-arm intervention trials and do not have a control group.

NIH often prefers placebo control groups for efficacy and effectiveness trials, but this type of control group might not be in the best interest of rehabilitation research. A usual care control group might be acceptable instead of a placebo group if providers cannot be influenced by knowing whether patients received the new treatment. However, in mild TBI (for instance), the outcomes of interventions are usually subjective, and patients' beliefs about which treatment they received could influence their outcomes.

These and other suggested white paper topics within the Design Considerations domain were:

- Characteristics of different types of control groups (e.g., standard care, usual care, no treatment, and placebo)
- Acknowledgement that regression to the mean often drives the control group's response more than placebo response
- Realistic expectations for outcomes from rehabilitation interventions that are not based on those for medications
- Impact of developmental spectrum on the design of clinical trials in children
- How to
 - Identify the research phase or stage
 - Assess multimodal versus unimodal interventions in clinical trials
 - Choose a clinical trial design
 - Conduct clinical trials and what to expect
 - Choose an appropriate control group while acknowledging that a placebo group is inappropriate for most rehabilitation trials

Evolving Topics and Considerations in Clinical Trials

Topics in this session included standardized documentation of interventions in studies to ensure treatment fidelity and the need for fidelity checks for multisite trials of a single intervention. The Template for Intervention Description and Replication checklist and guide (which could be included in a white paper appendix) offers one way to describe interventions so as to make study results interpretable and support replication studies and meta-analyses.

Concerns include the impact of how treatment is delivered during research (e.g., by a physical therapist) that is not part of the actual treatment (e.g., 10 minutes of exercise a day). Capturing this type of information is also critical. At the same time, however, it is important to remember that collecting all of the additional data mentioned at this workshop has a high cost.

These and other suggested white paper topics within the Evolving Topics and Considerations domain were:

- Inclusion of biostatisticians in each research team from the beginning
- Collection of information on how treatment is delivered
- Key aspects of treatments to measure for fidelity
- Template for Intervention Description and Replication checklist and guide in an appendix

- Need to let research questions drive clinical trial designs
- Integration of other disciplines, including implementation science and behavioral psychology, into rehabilitation trials

Critical Staff

Topics in this session were the roles and responsibilities of critical staff members, training requirements, and budget implications, all of which are related to the size of the trial, its phase, and the number of study sites. Another topic was the use of blinded assessors who are independent from study sites in multisite trials. Who delivers the intervention depends on the research question and whether the study is assessing efficacy or effectiveness.

These and other suggested white paper topics within the Critical Staff domain were:

- Roles and responsibilities of clinical trial personnel
- Training needs
- Personnel budget
- Blinded assessors
- Research coordinator selection and qualifications, including certifications and professional training
- How to select the right interventionist
- Standardization of documents and processes, especially in multisite studies
- Mechanism to support discussions and coordination among study personnel at different sites

Recruitment and Retention

Trial complexity influences recruitment and retention, and investigators need to design a recruitment plan just as they need to design their study. This plan identifies the target population, strategies to recruit that population, recruitment barriers, and how to overcome these barriers. The plan also addresses how to monitor recruitment and provides a monitoring timeline with short-term and long-term goals as well as resources for recruitment. Similarly, investigators need retention plans. Developing a recruitment plan with experts is as important at the beginning of a study as consulting a biostatistician to design the study. A recruitment/retention plan might be even more important than a study design—without participants, a study will have no data to analyze.

Suggested white paper topics within the Recruitment and Retention domain were:

- Recruitment barriers and facilitators along with ways to overcome these barriers
- Recruitment plan
- Retention plan
- Recruitment and retention of minority participants
- How patients prefer to be contacted about studies
- Appendix of successful recruitment and retention strategies
- Forum for investigators to discuss recruitment and retention strategies

- Dissemination of trial results to participants and referring physicians

Data Entry and Management

Suggested white paper topics within the Data Entry and Management domain were:

- Data collection that is as lean and close to the source as possible
- Use of centralized systems to allow real-time data entry, feedback, scheduling, and identification of outliers
- Training and retraining requirements
- Use of EHR data in clinical trials
- Standardized data collection methods
- Use of common data elements and other approaches to promote data sharing across trials
- Creation of a library of standardized data forms
- Use of technology to make clinical trials more efficient

Data and Safety Monitoring

Regardless of study type, investigators must determine at the beginning of their study who will monitor safety. The role of each person or group in protecting safety must be clear. Technology can be useful for ensuring that reported events are automatically sent to those who need this information.

Masking the DSMB can prevent knowledge of the trends in outcomes from influencing the DSMB's decisions about changes to study designs. However, the investigators, not the DSMB, should be responsible for design changes. Furthermore, masking the DSMB might mean missing some safety signals. Weighing the potential risks and benefits of any efficacy signal with a safety signal requires knowledge of what one is looking at. The DSMB statistician needs to understand what the data being reviewed mean, and DSMBs need members who will not overreact to a minor safety signal.

These and other suggested white paper topics within the Data and Safety Monitoring domain were:

- Most appropriate entity or individual to monitor safety for different types of trials
- Responsibilities of various individuals and groups in monitoring and reporting on safety
- Standardization of IRB requirements
- Whether DSMBs should be masked
- NIH institute and center rules for DSMBs
- DSMB budget
- Independent statistician on the DSMB

Outcome Measures for Different Phases of Translation

Participants discussed concerns with applying the new NIH definition of clinical trials in the rehabilitation setting. For example, the phases of clinical trials are only appropriate when the

basic science questions have been answered in humans, and good biomarkers are available, which is not the case in rehabilitation.

These and other suggested white paper topics within the Outcome Measures domain were:

- Purpose of each phase of a clinical trial
- Appropriate outcome measures for different clinical trial phases
- Similarities and differences between clinical trial phases in rehabilitation and other medical fields
- Impact on rehabilitation research, using examples, of the revised NIH clinical trials policy and definition
- Appropriateness of moving to the previous or subsequent clinical trial phase without abandoning the research concept in rehabilitation
- Need to discard some interventions that do not show early promise

Technology

Suggested white paper topics within the Technology domain were:

- Use of technology for
 - Measuring activity and outcomes in rehabilitation research
 - Monitoring protocol compliance and treatment fidelity and for adjusting the protocol when needed
 - Validation
 - Positioning rehabilitation research in health care reform
- When to use technology and when not to use it
- Ethics of technology use, including privacy concerns and influence on outcomes

Inter-Individual Response Heterogeneity

Measuring the ingredients of interventions that investigators develop might be easier than measuring the ingredients of standard care because of its variability. The rehabilitation field needs a way to categorize and measure treatment ingredients.

Examples of homogeneous interventions that yield heterogeneous responses would be useful for researchers wanting to study heterogeneous responses. If interventions vary, then responsiveness will vary, which will make the data very complex.

Too many studies have found that a given population benefited from the intervention without exploring the reasons why. Investigators must be warned not to assume that association implies causation without testing this assumption. Biomarkers might not explain response heterogeneity.

General themes emerging from discussion:

- Categorization and measurement of treatment ingredients
- Inter-individual response heterogeneity in rehabilitation research
- Response heterogeneity as a primary outcome that can be used to generate hypotheses

- Revisit existing data instead of conducting additional trials to explore response heterogeneity
- Value of negative trial results, which do not mean that nothing happened
- Extent of variability in usual care as a research topic
- Examples of homogeneous interventions that yield heterogeneous responses
- Impact of varied interventions on data complexity
- Exploratory analyses
- Planning for heterogeneity (e.g., impact on sample size power)
- Balance between tightening the inclusion and exclusion criteria to study heterogeneity and the need for generalizable results

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