Support for Clinical Trials at the National Center for Medical Rehabilitation Research and the NIH

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Importance of Clinical Trials

- Documenting the impact and efficacy of interventions
- Improving clinical practice
- Justifying patient reimbursement
- Improving clinical trial design across the NIH:
  - Real-world validity
  - Connecting to the goals and needs of the patient
  - Optimizing use of behavioral and psychosocial supports
  - Understanding role of environmental factors and confounds
  - Recruitment and compliance
  - Durability of effects
  - Clinically- (not just statistically-) significant outcomes

Unique Issues in Rehabilitation Trials

- Defining and operationalizing the active ingredient(s)
- Appropriate contrast/control groups
- Supporting and documenting patient compliance
- Outcomes may include:
  - Functional improvement
  - Participation
  - Health care utilization
- Accounting for unique patient factors:
  - Premorbid health and secondary conditions
  - Medications and concurrent treatments
  - Goals, motivations, and resources
- Environmental factors: barriers and supports
- Health care constraints and reimbursement

Research Opportunities and Needs

- Extending acute treatments to chronic patient populations
- Extending treatments to more diverse patient populations
  - Patients categorized by impairment rather than diagnosis
- Integrating more complex treatment packages, including:
  - Therapeutic exercise
  - Electrophysiology and magnetic stimulation
  - Assistive technologies
  - Pharmacological treatments
- Targeting the appropriate patient populations
  - Maximize the potential for demonstrating efficacy
  - But providing generalization to more diverse clinical populations

Proper Contrast Groups

- Based on active ingredient and proposed treatment theory
- Standard of care: highly variable and could be inadequate
- Historical controls: but are they still valid
- Activity control – balanced to the treatment
- Also balance for clinical and psychosocial support
- Consider Placebo effects and patient perceptions

- **Don't underestimate the natural course of recovery and adaptation; changing patient goals**

Alternative Trial Designs

- Randomized double-blind trials
- Dosage studies
- Cross-over designs
  - With heterogeneity, patient serves as own control
  - Sufficient consideration of washout effects
  - Randomize ordering: A -> B and B-> A
- Adaptive trial design and “small N” studies
- Practice-based trials

Statistical Issues

- Power calculation: patient heterogeneity/proposed effect size
- Outcome measures valid for that patient population
- Recruitment strategies and patient drop-out
- Avoid overly restrictive, impractical inclusion/exclusion criteria
- Account for environment factors
- Independent Data and Safety Monitoring Board
  - Futility analyses or premature success
- Primary versus Secondary outcome measures
  - Avoid using too many (and overlapping) outcome measures
  - Use outcomes appropriate to level of intervention
  - Consider patient burden
- Post-hoc analyses

NIH Support for Clinical Trials

- NIH Clinical and Translational Science Awards (CTSAs) from National Center for Advancing Translational Sciences (NCATS)
- Clinical trial networks (e.g., NINDS Strokenet)
- Patient registries and databases
- Pilot studies and early-stage proof-of-concept studies
- Dosage studies (to optimal dosage and delivery strategy)
- NIH Clinical Trial Planning Grant (R34) – administrative issues

- **Medical Rehab Research Infrastructure Network:**
  - Outcomes and Assessment
  - Analysis of Large Data Sets ***www.NCMRR.ORG***
  - Future Interests (RFA-HD-15-010): Clinical Trial Design!

NIH Support for Clinical Trials

- Do not propose underpowered pilot studies
- Do not hypothesize unrealistically large treatment effect
- Do not rush to propose an efficacy trial when more studies on optimization of dosing and outcome measures are required
- Start with adequate statistical expertise and data management
- Cover appropriate Human Subjects issues
- Contact NIH Staff
  - Grant mechanisms and support strategies differ
  - May have special budgetary constraints
  - May have special pre-approval and application policy
  - Coordinate support among NIH Institutes