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0894-9115/08/8711-0937/0
American Journal of Physical Medicine & Rehabilitation

REPORT & REVIEW

The Physical Therapy Clinical Research Network (PTClinResNet)

Methods, Efficacy, and Benefits of a Rehabilitation Research Network

ABSTRACT

Winstein C, Pate P, Ge T, Ervin C, Baurley J, Sullivan KJ, Underwood SJ, Fowler EG, Mulroy S, Brown DA, Kulig K, Gordon J, Azen SP; Physical Therapy Clinical Research Network (PTClinResNet): The Physical Therapy Clinical Research Network (PTClinResNet): methods, efficacy, and benefits of a rehabilitation research network. Am J Phys Med Rehabil 2008;87:937–950.

This article describes the vision, methods, and implementation strategies used in building the infrastructure for PTClinResNet, a clinical research network designed to assess outcomes for health-related mobility associated with evidence-based physical therapy interventions across and within four different disability groups. Specific aims were to (1) create the infrastructure necessary to develop and sustain clinical trials research in rehabilitation, (2) generate evidence to evaluate the efficacy of resistance exercise–based physical interventions designed to improve muscle performance and movement skills, and (3) provide education and training opportunities for present and future clinician–researchers and for the rehabilitation community at-large in its support of evidence-based practice. We present the network's infrastructure, development, and several examples that highlight the benefits of a clinical research network. We suggest that the network structure is ideal for building research capacity and fostering multisite, multiinvestigator clinical research projects designed to generate evidence for the efficacy of rehabilitation interventions.

Key Words: Multisite Clinical Trials, Medical Rehabilitation, Outcomes Research, Disablement Model, Biomedical Informatics, Physical Therapy

Disclosures:

* Physical Therapy Clinical Research Network (PTClinResNet): The network's principal investigator is Carolee J. Winstein, PhD, PT, FAPTA, and the coprincipal investigator is James Gordon, EdD, PT, FAPTA (both at University of Southern California, Los Angeles, CA). Project principal and coprincipal investigators include David A. Brown, PhD, PT (Northwestern University, Chicago, IL); Sara Mulroy, PhD, PT, and Bryan Kemp, PhD (Rancho Los Amigos National Rehabilitation Center, Downey, CA); Loretta M. Knutson, PhD, PT, PCS (Missouri State University, Springfield, MO); Eileen G. Fowler, PhD, PT (University of California–Los Angeles, Los Angeles, CA); and Sharon K. DeMuth, DPT, Kornelia Kulig, PhD, PT, and Katherine J. Sullivan, PhD, PT (University Southern California, Los Angeles, CA). The data-management center is located at University of Southern California, Los Angeles, CA, and is directed by Stanley P. Azen, PhD. The four-member data safety and monitoring committee are Nancy Byl, PhD, PT, FAPTA, chair (University of California–San Francisco, San Francisco, CA), Hugh G. Watts, MD (Shriners' Hospital for Children–LA Unit, Los Angeles, CA), June Isaacson Kailes, MSW (Western University of Health Sciences, Pomona, CA), and Anny Xiang, PhD (University of Southern California, Los Angeles, CA).

The Foundation for Physical Therapy supported this work. The authors have no proprietary or commercial interest in any materials discussed in the manuscript.

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In 2002, the National Institutes of Health (NIH) charted a roadmap for medical research for the 21st century that included the development of research networks. The purpose of the roadmap was to identify major opportunities and gaps in biomedical research, and to include a vision and guidelines for implementation. The roadmap identified the need to "build better integrated networks of academic centers linked to a qualified body of community-based health care providers.[1]"

Concurrent with the NIH roadmap initiative, and to facilitate cost-effective access to health care, academic institutions are seeking ways to form partnerships that allow clinically relevant research to be carried out in an efficient and effective manner. The structure of a clinical research network was identified as an ideal model because it allows a distributed organization, composed of research teams and resources, to be combined in a strategic manner to efficiently and effectively move forward the clinical translational research enterprise.

Other funding agencies have recognized the potential for this research model. In particular, the Foundation for Physical Therapy raised the funds to develop a clinical research network that would advance the science supporting the effectiveness of physical rehabilitation interventions. In addition, because the physical therapy profession is undergoing rapid maturation as a doctoring profession, the expansion of research facilities and resources could serve the needs of the profession in achieving the status required for autonomous, evidence-based practice.

The NIH roadmap drives rehabilitation research toward the next critical step to refinement of its clinical practice by reengineering the clinical research enterprise. The next critical step for rehabilitation medicine, and the one that is presented in this paper, is to link together a group of leading interdisciplinary clinician–researchers and academic institutions in a novel model of cooperation through the creation of an integrative, coherent clinical research network.

Emergent from this goal, the Physical Therapy Clinical Research Network (PTClinResNet) was established in 2002. PTClinResNet consists of one coordinating center, five primary satellite sites, and two sets of outpatient clinics (Fig. 1). The network has three specific aims: to (1) create the infrastructure necessary to develop and sustain clinical trials research in rehabilitation, (2) generate evidence to evaluate the efficacy of resistance exercise–based physical interventions designed to improve muscle performance and movement skills, and (3) provide education and training opportunities for present and future clinician–researchers in rehabilitation and for the rehabilitation community at-large in its support of evidence-based practice.

In its original proposal, PTClinResNet used the Nagi disablement model[2] as a framework for outcomes analysis. However, the network has since adopted the International Classification of Functions, Disability, and Health (ICF, Fig. 2), in large part because of its acceptance by the broader community of healthcare professionals and its greater research potential to identify important interactions and links between outcome measures.[3] The ICF was approved in May 2001 by the World Health Assembly and is the successor to the International Classification of Impairments Disabilities and Handicaps (ICIDH). Using rules that specify links between items from specific instruments and corresponding ICF categories,[4] the representation of ICF components of body functions and structures, activities, participation, and contextual factors can be investigated. The ICF is currently being applied in clinical research and clinical practice in areas, including rehabilitation medicine.[5] The ICF classification is an effective organizational framework to allow assessment of outcome interactions that are associated with health-related problems (i.e., body

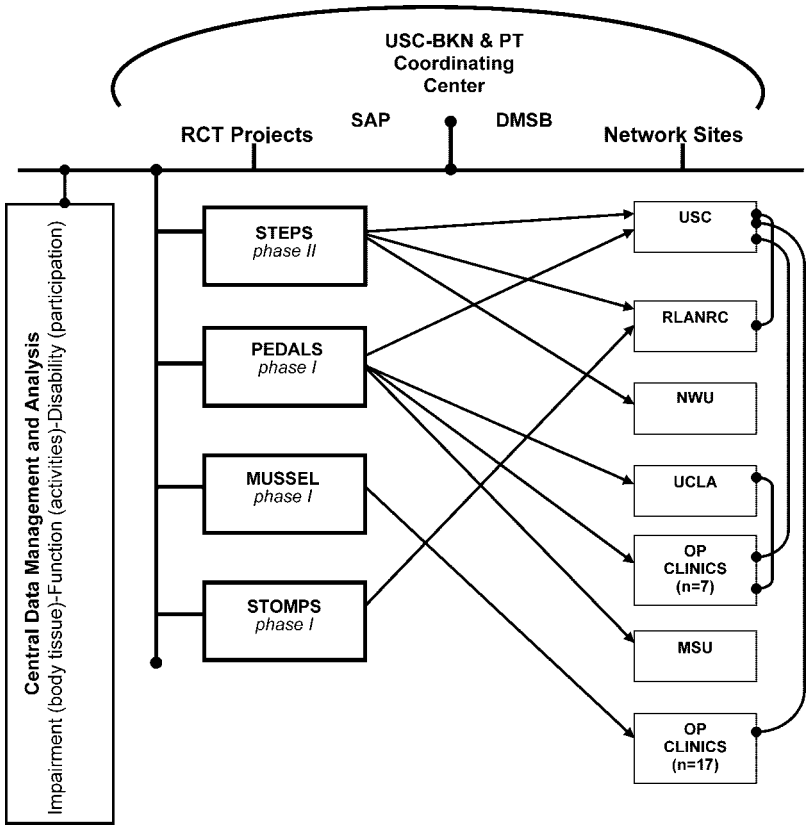

FIGURE 1 *The structure of PTClinResNet, with the umbrella coordination center providing oversight, data management, education, training, and fiscal management for the four projects (left column) that will unfold across five satellite sites, and two sets of outpatient clinics (right column). One box represents seven outpatient pediatric clinics associated with the PEDALS project, and the bottom box represents 17 different outpatient orthopedic clinics in the greater Los Angeles area, including USC PT associates associated with the MUSSEL project. Names of the clinics can be found in the Acknowledgments section. SAP, Scientific Advisory Panel; DMSB, Data Monitoring and Safety Board; STEPS, Strength Training Effectiveness Post Stroke; PEDALS, Pediatric Endurance Development And Limb Strengthening; STOMPS, STrengthening and Optimal Movements for Painful Shoulders in chronic spinal cord injury; MUSSEL, MUscle-Specific Strengthening Effectiveness post Lumbar microdiscectomy; USC, University of Southern California, Division of Biokinesiology and Physical Therapy; RLANRC, Rancho Los Amigos National Rehabilitation Center; NWU, Northwestern University, Department of Physical Therapy and Human Movement Sciences, Feinberg School of Medicine; MSU, Missouri State University, Department of Physical Therapy. The outside brackets of the network sites column illustrate the pre-network institutional and/or collaborative links between sites.*

function/structure impairments, activity limitations, participation restrictions) and across disease- or injury-specific health conditions.[3]

The purpose of this paper is to describe the methods and strategies used in accomplishing the initial goals of building PTClinResNet, along with a summary of its current status and unique benefits. Specifically, the Methods section will discuss the infrastructure and development process, including the rationale for a network coordinating center. Included are details about the different study designs, challenges for data acquisition, implementation, and data analyses. The Results section highlights examples and benefits of a network collaboration. These include example results of an exploratory meta-analysis afforded by the network's shared database and common disablement framework—specifically, across-project relationship(s) at baseline for health status and measures of disability severity. Finally, we describe examples of spin-off projects and an NIH-funded phase III clinical trial that successfully leveraged the PTClinResNet infrastructure. The discussion section summarizes the benefits of a clinical research network, including its inclusion in a national registry (Inventory and Evaluation of Clinical Research Networks, IECRN), and makes recommendations for how to avoid pitfalls and overcome barriers to the formation of clinical research networks for future rehabilitation research.

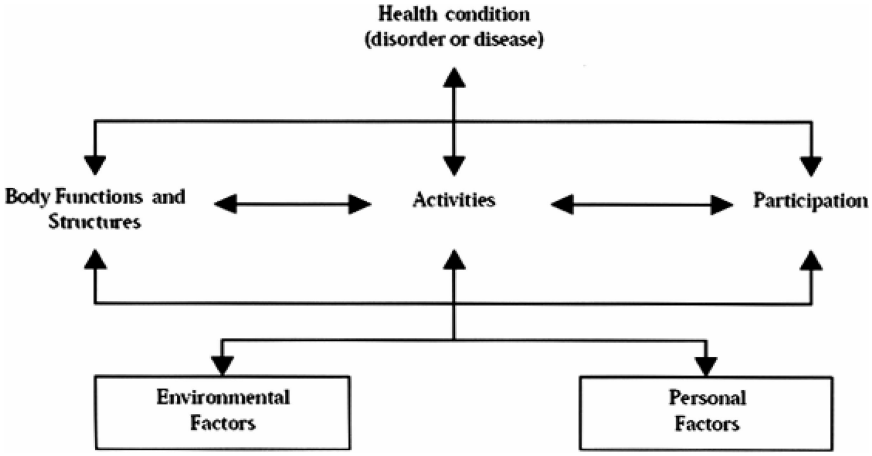

FIGURE 2 *Visualization of the current understanding of interaction of various components of the International Classification of Functioning, Disability and Health (ICF). The ICF does not model the "process" of functioning and disability. It can be used, however, to describe the process by providing the means to map the different constructs and domains. It provides a multiperspective approach to the classification of functioning and disability as an interactive and evolutionary process. It provides the building blocks for users who wish to create models and study different aspects of this process. In this sense, ICF can be seen as a language; the texts that can be created with it depend on the users, their creativity, and their scientific orientation.*[3]

CLINICAL RESEARCH METHODS IN REHABILITATION ARE DEVELOPING

Clinical trials research in rehabilitation medicine is a relatively underdeveloped area of focus for clinician–scientists in rehabilitation fields.[6] In response to a growing need for the development of evidence-based approaches in rehabilitation, one of the first 2-day workshops on this topic was conducted in 1998 by the National Advisory Board on Medical Rehabilitation Research of the NIH–NICHD–NCMRR clinical practice programs. The workshop, Clinical Trials in Rehabilitation, was divided into four main sessions: (1) outcome measures, (2) clinical trial design and selected disorders, (3) challenges in rehabilitation clinical trials, and (4) recommendations. To a large extent, the formation, mission, and design of PTClinResNet were motivated by an understanding of the principles, challenges, and barriers, and they are consistent with conclusions that emerged from that workshop. More recently, the American Journal of Physical Medicine and Rehabilitation has published an entire supplement devoted to the topic of clinical trials in medical rehabilitation that summarizes a later conference held on the same topic 5 yrs ago in 2002.[7]

A COMMON THEME

One of the initial aims of PTClinResNet was to generate evidence to evaluate the efficacy of physical therapy interventions. To accomplish this, we proposed four projects; one multisite phase II randomized clinical trial (RCT) and three phase I RCTs. Each of the four projects focused on a different disability group (adult stroke, pediatric cerebral palsy, chronic spinal cord injury, and low-back disorder) and identified and tested physical therapeutic strategies for improving function and participation. The common theme adopted by each RCT was to design a therapeutic intervention study that was based on the best available evidence and that used a dynamic task-oriented or muscle-specific approach to enhancing muscle performance. When completed, this comprehensive set of investigations is expected to provide practical clinical guidelines for rehabilitation practitioners that will include recommendations for optimal intervention strategies for a variety of conditions, and to provide evidence that the intervention strategies are effective in typical clinical settings.

THE ICF CLASSIFICATION PROVIDES A FRAMEWORK FOR PTCLINRESNET

Because of recent concerns for healthcare cost containment and appropriate healthcare utilization, clinical outcomes in rehabilitation research have shifted toward investigations of interventions that improve outcomes at the level of individual function, participation, and quality of life (QOL). Clinical outcomes research in rehabilitation medicine has progressed from earlier work, which focused exclusively on the impairment (body function/structure) level, to more recent work, which focuses on outcomes at the activity-limitation or participation-restriction level. With a growing body of evidence demonstrating the efficacy of physical

therapy treatments,[8–11] there is clearly a paradigm shift in rehabilitation research from descriptive studies at each classification level to that which provides "direct evidence of the degree to which physical therapy that affects an impairment (e.g., muscle force) will also reduce disability and improve the functional outcomes of the patient (i.e., in activities such as transfers, walking ability, and improved quality-of-life."[12 (p968)]

Current trends in physical rehabilitation intervention effectiveness include the use of outcome measures that are not just limited to body structure or function impairment (e.g., muscle function) or activity restriction (e.g., reduced walking velocity) but that also include measures that reflect a person's participation in meaningful life roles as measured by components of health status such as the SF-36 and, more broadly, subjective QOL. Evidence of this paradigm shift is evident in the rehabilitation research literature, with more studies using outcome measures that relate to the various classification levels of the ICF model.[13] The medical community recognizes the importance of measuring and addressing patient-reported outcomes (including QOL) and recognizes the need to improve the measurement of these factors for different disability groups.[14,14a]

With each RCT hosted within the network, there is at least one outcome specific to each of the major levels of the ICF framework (body function/structure, activities, participation). Primary outcomes are those that are highly reliable, valid, and study specific (disability, population, specific aim). Further, primary outcomes are the ones that were used for preproposal sample size estimates and that, accordingly, are thought to be those outcomes most directly influenced by the intervention. Additionally, each study included a set of secondary outcomes using study-specific measures at each major ICF level. Three studies used a common overall measure of health status (i.e., SF-36), whereas the pediatrics RCT (PEDALS) used a similar but disability-specific health-related QOL measure (i.e., PedsQL). Overall, and for each of the four RCTs, we are testing the hypothesis that a specific physical intervention that enhances muscle performance and functional movement skill can reduce movement-related body structure impairment and enhance functional performance and participation, and, in so doing, have a positive effect on health status, participation, and/or QOL.[15]

METHODS

PTClinResNet is organized through a center that coordinates each project's RCT development and implementation. The center's infrastructure allows for centralized project design, project management, and data analysis across the current four clinical trials and multiple sites participating in the network. In addition, the center provides a forum for investigators with a common interest in rehabilitation research to share their expertise. This multidisciplinary collaboration allows network nodes (i.e., clinical trials and sites) accessibility to specialized resources, including biomedical informatics and biostatistics.

An important function of the coordinating center is to develop standardized project protocols and data-collection instruments that are consistent and easily accessible from any network node. For PTClinResNet, a uniform standardized data dictionary was defined, allowing for multisite data entry and analysis and across-study comparisons. Building from this design, it was possible to generate comprehensive reports on project development progress, participant safety, and dataset completeness. Effective communication is a key factor in a network with multiple studies and research sites that are located across large metropolitan areas as well as across the country. The network coordinating center facilitates communication between network investigators and clinicians and provides general information to the public sector. This was accomplished through the PTClinResNet Web site (http://pt.usc.edu/clinresnet). The Web site contains unrestricted information available to the physical rehabilitation professional community and potential study participants, and it also provides an overview of the network, including relevant news items, conference information, and, more recently, our dissemination efforts. A document-management system is available for network investigators and clinicians to share secure documents. Monthly steering committee meetings allow investigators and management personnel to address organizational issues and plan future network activities.

A clinical research network can provide essential management oversight that can more effectively organize time constraints, determine network priorities, define individual project scope, and monitor resource use. Ultimately, effective management is needed to achieve research aims. The coordinating center provided project management tools to assist PTClinResNet personnel in reaching the network objectives. One important tool, the virtual help desk, was developed to prioritize and assign network needs to the appropriate data-management personnel. This mechanism improves quality of service and provides a quantitative measure of effort. Project scheduling is also important, to determine the critical path of activities needed to reach network goals. Quality-control reporting, along with primary and secondary data analyses, is implemented chronologically according to timelines reflected in the project schedule. Project

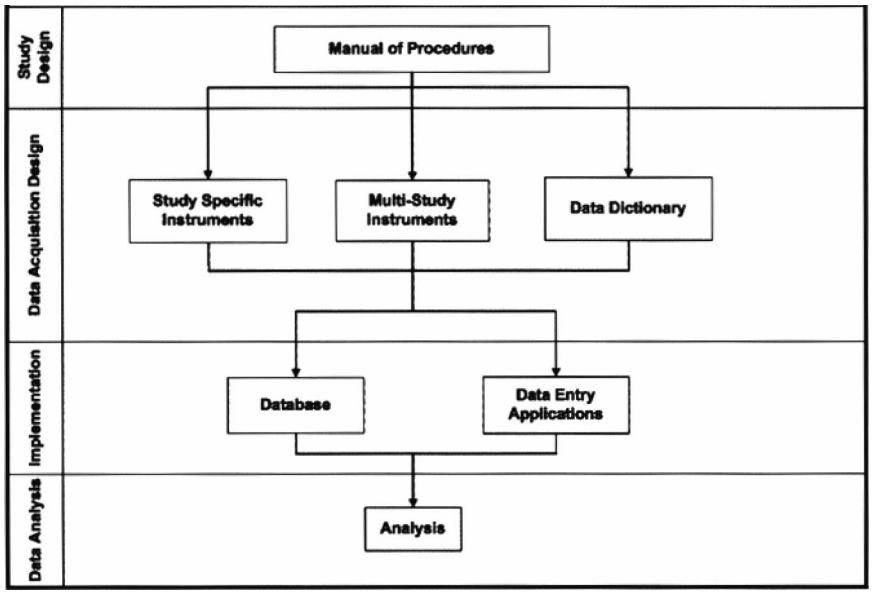

FIGURE 3 *The PTClinResNet development process. The rows in the figure represent the phases of the development process (study design, data-acquisition design, implementation, and data analysis). The boxes are deliverables developed during each phase, and arrows show the relationships these deliverables have on later phases in the development process.*

management tools are available to graphically represent activities and deadlines.

In addition to project management, infrastructure development for the network included the implementation of a study data-acquisition and data-management plan that included the following four elements: study design, data-acquisition design, data-management implementation, and data analysis (Fig. 3). The following describes each element of this aspect of the infrastructure development.

Study Design

The project investigators developed specific measurement and intervention protocols that are documented in a common manual of procedures (MOP). The purpose of an MOP in clinical trials is to organize the design of the project, standardize measurement methods, and ensure consistent application of intervention protocols. The MOP served to train and standardize the evaluators and interventionists. Each site within the network can access the MOP(s) on the secure area of the PTClinResNet Web site. Access to each of the four MOPs by all network investigators fostered systematic and common practices across the sites for everything from participant enrollment and randomization to data entry, and regulatory operations such as maintaining IRB-approval tracking and reporting adverse events. Similarly, various protocols and standardization criteria were developed by one study team that were adapted or modified by another study team.

Data-Acquisition Design

By using the MOP and collaborating with project investigators, the coordinating center developed the data-collection instruments. In PTClinResNet, four classifications of data-collection forms were devised: participant information, evaluation, intervention, and adverse events. In addition to participant data, each form contains information on administration of the instrument, versioning, and relevant explanatory comments. Data instruments shared across studies were designed to be used network-wide (e.g., SF-36 was used for all adult participants).

Once all data-collection forms were finalized, the data dictionary was developed. The data dictionary is a structure that stores metadata. The data dictionary serves a twofold purpose: creating the database, and functioning as documentation for data analysis. The data dictionary includes a descriptive variable name, the data type (integer, character, decimal), the specific question as it seems on the data-collection instrument, and the coding and quality-control parameters for every variable. As an example, (a) variable name = gender, (b) data type = integer, (c) question on form = what is the participant's gender? (d) codes = 1 (male), 2 (female), (e) field length = 1 digit, and (f) quality control = required data point.

Data-Management Implementation

After a thorough analysis of the project and data-acquisition designs, we implemented a data-management system consisting of the PTClinRes-

Net database and Web-based data-entry applications for each project. The database is designed to follow a relational model, with each dataset representing a data-collection instrument. Studies that shared data-collection instruments had common datasets. The database was normalized to avoid data redundancy and to allow scalability in the size of the dataset. A dataset record represented the measurement for a specific participant at a particular time point (e.g., baseline evaluation, postintervention).

The Web-based applications allowed database transactions (i.e., the entry of data from the data-collection form to the structured query language (SQL) database, or the exporting of data from the SQL database to a SAS or SPSS database for analysis and/or reporting purposes). This software was designed to facilitate quick and accurate data entry from the hard-copy data-collection forms. The applications were programmed to ensure data quality and user-level security, and to ensure database integrity. The data-entry application allowed the therapist to create a new or find an existing participant. For new participant identifications, the system required clinical information and project inclusion and exclusion data to be entered, to confirm participant eligibility. The participant summary page displayed important participant information and tracked their progress in the clinical trial (e.g., visits, evaluations). The applications included a global menu that remains constant for quick navigation between data-entry sections. A quality-control feature used metadata from the data dictionary to prevent common errors, such as permissible range (i.e., minimum, maximum) in the data dictionary to prevent or challenge potential outliers.

Data Analysis

The Web-based applications and statistical software interfaced with the database through SQL. Various types of relationships were defined in SQL to join participant-enrollment data with information, evaluation, and intervention data. This allowed tracking and reporting of participant progress through the project, customized datasets for statistical analysis, and enhanced cross-dataset integrity checks. Data analysis was performed using advanced statistical software tools that included SAS version 8.2, R Statistical Language version 2.1.0, and SPSS version 13.0.

In addition, the research network facilitates interactions between the investigative team and the statistical team through steering committee meetings, or through smaller subgroup discussions including PIs and data-management center (DMC) personnel. Productive interactions include (a) modifying analytic plans for specific hypotheses because of unexpected covariates, noncompliance of study participants, unexpected distributional characteristics, etc., and (b) the identification and recommendation of analytic plans for secondary analyses, including subgroup analyses, identification of prognostic factors within a given treatment group, identification of treatment × mediating variable interactions, etc.

RESULTS

In this section, we briefly summarize the current RCTs hosted by PTClinResNet, the benefit of a research network for comparisons across studies, and an overview of exemplar spin-off studies, including a phase III clinical trial that leveraged the infrastructure described in the Methods section.

Current Clinical Projects Hosted on PTClinResNet

Figure 1 illustrates the four ongoing clinical projects that are hosted on PTClinResNet: (1) Strength Training Effectiveness Post-Stroke (STEPS) is the network's flagship project, being the only phase II RCT currently hosted. The primary objective is to determine whether functional walking outcomes in individuals with chronic stroke are improved with exercise programs that include task-specific (i.e., body weight–supported treadmill training) or lower-extremity strength training, or a combined exercise program that includes both task-specific and strength training. (2) Pediatric Endurance and Limb Strengthening in spastic diplegic Cerebral Palsy Children (PEDALS) is a phase I investigation with a primary objective of determining the efficacy of a stationary cycling intervention for treatment outcomes in children with cerebral palsy. (3) Muscle Specific Strength Training Effectiveness after Lumbar Microdiscectomy (MUSSEL) is a phase I investigation to assess the immediate and long-term effects of muscle-specific strengthening on decreasing disability and improving function and QOL in persons recovering from lumbar microdiscectomy. (4) Strengthening and Optimal Movements for Painful Shoulders in Chronic Spinal Cord Injury (STOMPS) is a phase I investigation with a primary objective of determining the efficacy of a combined intervention comprising strengthening exercises and instruction in optimal movements for painful shoulders in persons with chronic spinal cord injury.

Baseline Health Status and Severity Across RCTs

For each clinical trial, outcome measures of function, disease- or injury-specific health status, and a common measure of health status (e.g., SF-

TABLE 1 Significance and effect sizes of health status across function, pain, and disability severity levels

a. STEPS: SF-36 and SIS Health Status Scores Stratified by Severity of 10-m Walk Test[38]					
Health Status Score	**n1/ n2**	**Severity Category 1, SSV ≥ 0.5 m/s**	**Severity Category 2, SSV < 0.5m/s**	**ANOVA P Value**	**Effect Size**
SF-36 physical[16]	35/24	41.4 (7.4)	37.8 (8.5)	0.08	0.49
SF-36 mental	25/24	54.5 (9.6)	52.0 (11.4)	0.36	0.26
SIS-16[17]	44/32	61.9 (14.8)	49.9 (16.1)	0.001	0.80

b. PEDALS: PedsQL Health Status Scores Stratified by Severity of GMFCS[20]					
PedsQL Health Status Score 21	n1/n2	Severity Category 1, GMFCS Levels I and II	Severity Category 2, GMFCS Level III	ANOVA P Value	Effect Size
Physical functioning	32/30	75.2 (19.3)	58.4 (21.1)	<0.01	0.87
Emotional functioning	32/30	69.5 (22.9)	61.3 (22.5)	0.16	0.36
Social functioning	32/30	72.0 (21.1)	60.5 (21.1)	0.04	0.54
School functioning	32/30	70.2 (18.2)	57.3 (19.2)	0.01	0.70
Psychosocial health summary score	32/30	70.6 (17.3)	59.7 (16.8)	0.02	0.62

c. MUSSEL: SF-36 Health Status Scores Stratified by Severity of pain VASs[39]					
Health Status Score	n1/n2	Mild, 1 to <5	Moderate/Severe, 5 to 10	ANOVA P Value	Effect Size
SF-36 physical	87/13	36.5 (8.2)	27.6 (4.3)	<0.0001	1.08
SF-36 mental	87/13	49.6 (10.8)	47.2 (9.9)	0.46	0.22

d. STOMPS: SF-36 Health Status Scores Stratified by Severity of WUSPI[18]					
Health Status Score	n1/n2	Severity Category 1, 2.9 < 46.3	Severity Category 2, 46.3–124.9	ANOVA P Value	Effect Size
SF-36 physical	38/37	39.0 (8.7)	31.5 (7.4)	0.0002	0.86
SF-36 mental	38/36	57.6 (9.2)	46.7 (12.7)	0.0001	1.18

n1/n2, sample sizes for less severe vs. more severe categories; SSV, self-selected overground walking velocity; SIS, Stroke Impact Scale[17]; GMFCS, Gross Motor Function Classification System[20]; PedsQL, Pediatric Quality of Life Inventory[21]; VAS, visual analog scales; WUSPI, Wheelchair Users Shoulder Pain Index.[18]

36[16]) were used. Table 1 uses baseline data and summarizes the results of an exploratory omnibus analysis to compare the effect sizes for various health status scores (e.g., physical, mental) stratified by function, pain, or disability severity levels for each of the four projects. The effect size was calculated as the difference in the mean health status scores (more severe − less severe) divided by the standard deviation of the health status scores for the less severe (impaired) group.

Because physical health was the primary health-related variable that was impacted by severity classification across all four studies, we contrasted the impact of severity on physical health using the common metric of effect size (Fig. 4). For the SF-36,[16] the physical health domain is a composite of four subscales: bodily pain, role physical, general health, and physical functioning. Effect sizes ranged from 0.49 (STEPS) to 1.08 (MUSSEL), demonstrating the impact of the condition's severity on physical health. The large effect size in the postsurgical acute low-back disorder group (i.e., MUSSEL) as compared with the moderate effect size in the chronic stroke groups (i.e., STEPS) is not surprising, given that the physical health domain of the SF-36 has a large component related to bodily pain. This comparison reflects the added sensitivity that all components of the physical health domain may have on a health condition such as a low-back disorder, and the decreased sensitivity in a health condition such as chronic stroke, where impaired mobility has a greater impact on physical health than pain. In contrast, the effect size for the SIS-16,[17] in the chronic stroke

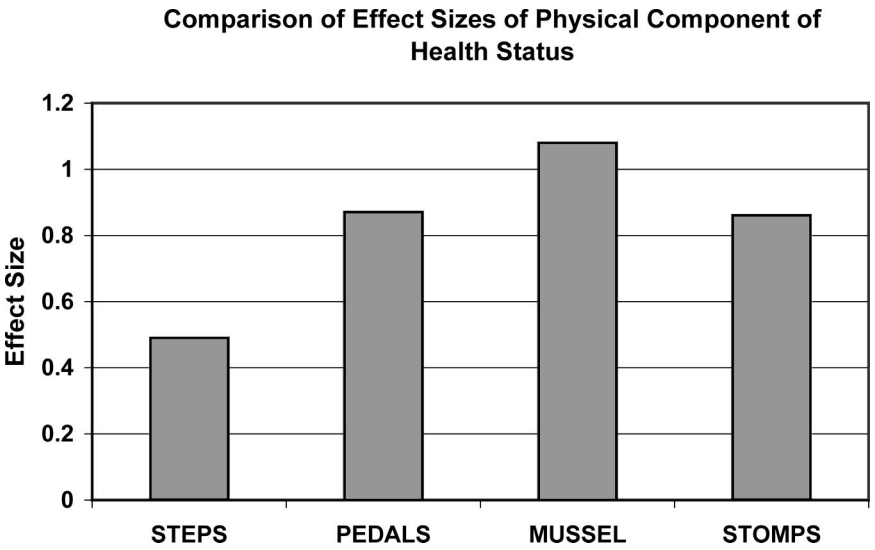

FIGURE 4 *Impact of disability on HRQL physical health score, using effect sizes for the four projects hosted by PTClinResNet. A comparison of the effect sizes for physical health status scores across the four projects: STEPS, PEDALS, MUSSEL, and STOMPS. The effect size was calculated as the difference in the mean physical component scores (more severe − less severe) divided by the standard deviation of the physical component for the less severe group. HRQL, Health-Related Quality of Life; STEPS, Strength Training Effectiveness Post Stroke; PEDALS, Pediatric Endurance Development and Limb Strengthening for children with cerebral palsy; MUSSEL, Muscle-Specific Strengthening Effectiveness post Lumbar microdiscectomy; STOMPS, Strengthening and Optimal Movements for Painful Shoulders. STEPS, MUSSEL, and STOMPS effect size measurements are based on the physical health score of the SF-36, and the PEDALS effect size measurement is based on the physical functioning subscale of the PedsQL).*

study was high (0.80), which illustrates the importance of including disease-specific health status instruments as well as more general instruments of health status (Table 1a).

For STOMPS, the effect size of initial pain level on the physical health scale of the SF-36 was intermediate between that of the STEPS and MUSSEL studies. For the subjects in STOMPS, the initial WUSPI[18] scores were moderately correlated with both the bodily pain and the role physical subscales of physical health, but they were less strongly linked to the general health and physical function subscales.[19] This indicates that shoulder pain is impacting the participants' ability to fulfill the physical demands of their life roles. The physical function subscale is less affected by shoulder pain, however, because several of those activities are related to walking and stair climbing, which are limited by the spinal injury itself, but not the shoulder pain. In contrast, for individuals with a low-back disorder (i.e., MUSSEL), the relationship between pain levels and walking function would be expected to be more strongly linked.

The severity categories used for PEDALS contrasts children who are able to walk independently without assistive devices (GMFCS levels I and II)[20] vs. those who require walkers or canes (GMFCS level III).[20] The physical functioning scale score of the PedsQL[21] is focused on a child's ability to walk, run, play, lift heavy objects, and perform chores. All of these functions are greatly affected by functional mobility and explain the high effect sizes shown in Table 1b and Figure 4. Two other scale scores, social functioning and school functioning, include items that are related to functional mobility and severity of disability, such as the ability to keep up with others at play and missing school for medical appointments. These scales also demonstrate significance between severity groups based on GMFCS level with relatively large effect sizes. In contrast, the emotional functioning scale score did not demonstrate significance between severity groups or a large effect size. This subscale focused on the child's feelings and did not include any questions related to physical function.

Spin-off Projects and a Phase III RCT Using the Network Infrastructure

One important benefit of a clinical research network is the opportunity to leverage the infrastructure for future clinical trials. Investigators associated with PTClinResNet (K. Sullivan, S. Azen) were recently awarded an NIH clinical trial grant from NINDS to conduct a phase III definitive RCT, Locomotor Experience Applied Post-Stroke (LEAPS; NIH/NINDS/NCMRR NS05056, P. W. Duncan, PI). The primary goals of the LEAPS trial are to determine whether a specialized locomotor

training program that includes use of a body weight–support system and a treadmill as a treatment modality will result in a functionally significant improvement in 1-yr walking outcomes of individuals after stroke compared with a nonspecific, low-intensity exercise comparison group. The LEAPS trial will also address whether the timing of therapy, severity of impairments, and number of treatments affect outcomes. Components developed for PTClinResNet, including the standardized measurement and intervention protocols and resources from the infrastructure, were integrated into the LEAPS MOP to build the multisite database for data entry, standard report generation (e.g., actual vs. projected recruitment, quality-control reports, posting of steering committee minutes), and a discussion board to facilitate investigator communication.

Several other spin-off studies also used tools that were initially developed for PTClinResNet. For example, a study recently funded by NIDDR (D. Brown, co-lead investigator, STEPS) used the body weight–support treadmill training protocol and the standardized measurement procedures developed for STEPS to investigate the use of a virtual reality system for improving walking outcomes during treadmill training in people poststroke (NIDRR H133G050132). Sara Mulroy (co-lead investigator, STOMPS) was recently awarded a 5-yr NIH grant from the National Center for Medical Rehabilitation Research (NCMRR HD049774) to study the risk factors for shoulder pain in patients with spinal cord injury.

At the coordinating institution, federated databases are being developed from elements of the DMC for PTClinResNet to integrate clinical, magnetic resonance imaging, and functional magnetic resonance imaging data, with the goal of promoting interesting data queries to better understand the mechanisms associated with improvement in treatment outcomes. This work has been fueled by an NIH Roadmap initiative to promote exploratory centers for interdisciplinary research. Our project aims to establish a center for new directions in stroke rehabilitation (RR-04-002, T. McNeill, PI; C. Winstein, co-PI).

DISCUSSION

Clinical Trials Research Will Benefit from Clinical Trial Network Collaboration

The team of scientists collaborating under the umbrella PTClinResNet is a diverse group of researchers whose primary research training provides expertise across relevant but diverse disciplines including biomechanics, kinesiology/movement science, clinical psychology, health services, and neurorehabilitation. This team of clinical scientists has established track records that can be leveraged for the design and testing of optimal rehabilitation interventions. In other words, the collaborative team is well suited to translate the relevant science into clinical practice in rehabilitation medicine. In addition, the uniform structure permits leveraging the leadership and strategies of the phase II flagship RCT to the other three phase I RCTs.

We suggest that foundational research in the social, cognitive, and neurosciences can have a useful, long-lasting impact on the development of theoretically defensible rehabilitation practices.[22] Historically, physical rehabilitation practice evolved in part from practical needs (e.g., WWII injuries) and was influenced primarily by a physiologic/medical perspective. The need to foster translation of the biological and physical sciences into clinical practice has been recognized for some time in medical education.[23,24] Recently, we have seen in several cases that preclinical work using animal models of injury have begun to influence the development of new practices of rehabilitation. This is most evident from the introduction of such interventions as constraint-induced movement therapy for upper-extremity recovery in stroke[25,26] and body weight–assisted gait training in spinal cord injury[27] and stroke.[28] However, the progression from discovery to preclinical to phase III RCT can be protracted.[29] For example, the recently published phase III EXCITE trial of constraint-induced movement therapy is the first multisite randomized trial to demonstrate the efficacy of a rehabilitative intervention. In so doing, it moves neurorehabilitative care into the area of evidence-based medicine.[30,31] However, the EXCITE results were published 25 yrs after the first case study to apply constraint-induced movement therapy, and 17 yrs after the first phase I clinical trial study[32] designed to test the feasibility and efficacy of this approach in hemiparetic adults. We suggest that one important benefit of a clinical trials network with its collective expertise of the investigative team and the centralized data-management infrastructure is to provide the means for more efficient and effective progression through the translational steps of clinical research to evidence-based practice.

Other benefits of the PTClinResNet network collaboration have included (1) the opportunity to investigate interactions within and between disability groups. The shared ICF framework with some shared outcome measures such as the health status inventory, SF-36, allow for exploratory analyses across disability groups; (2) an opportunity to provide education and training to a wide array of students, professionals, and junior investigators; and (3) an opportunity to impact clinical practice through clinic-based research that requires standardization of assessments and intervention protocols. To this end, several of the network investiga-

tors have begun to disseminate descriptions of the clinical protocols through the open-access BMC journal.[33] Furthermore, the network served as a resource for a multisite study on the diagnosis referral process to physical therapy.[34]

Contributions of the PTClinResNet Scientific Team

The network investigative team comprises the network PI and co-PI, project lead investigator, co-leads, director of the data-management center, network project manager, clinical research coordinators, blinded/masked evaluators, intervention therapists, and an extensive group of data-entry personnel. Benefits of a comprehensive investigative team such as this include not only the opportunities for multisite and multidiscipline collaboration, but the practical aspects of increased participant-recruitment potential, thereby facilitating the attainment of larger sample sizes, which are necessary for more robust tests of effectiveness. The network is one way to overcome the single biggest problem in clinical trial research: failure to recruit to target goals.[35] In addition, the multidiagnostic database lends itself to various forms of meta-analysis across diagnoses, geographical regions, ages, and demographics (see, for example, Fig. 4). By responding to the NIH Roadmap recommendation for clinical research networks (and teams), PTClinResNet and the investigative team placed itself at the forefront of clinical research designs in rehabilitation, which, in turn, was successfully leveraged for a phase III definitive RCT (LEAPS).

PTClinResNet Is a Member of a National Registry

PTClinResNet is a recognized member of the Inventory and Evaluation of Clinical Research Networks (IECRN).[36] The IECRN, a component of the NIH Roadmap, is an inventory of health-related clinical research networks that have established requirements. For example, a clinical research network must conduct human subjects research that is relevant to improving the quality of human health, have scientific leadership that evaluates research ideas, and have a minimum of three independent entities. To date, there are 241 registered networks at IECRN. Of these, PTClinResNet is one of only a handful of these networks designed to address postacute repair, recovery, and rehabilitation.

Recommendations for Development of Future Networks

In retrospect, we appreciate that many lessons were learned during the development and implementation process. From the study-design phase, we recommend implementation of a policy that requires all data-collection forms to be designed for the user (evaluator/intervention therapist), to ensure that the paper-based form and Web-based data-entry screen are as consistent as possible. This policy will eliminate "guesswork" for the data-entry personnel and will prevent at least one source of error in the data-entry process. When forms are updated during the trial, we recommend immediate Web posting and automated e-mail notification to all appropriate personnel of the updates and any form changes, to ensure that the latest and most updated version is used.

At the data-implementation phase, we recommend immediate data entry and data checking after data collection, with no more than a 10-day delay between acquisition and entry. Many of the data-entry and analysis problems we encountered were attributable to an unintentional delay between collection/acquisition and data checking. For example, data-entry persons would find missing values in the data-collection form and have to try to track down the evaluator, who may have left the project or did not remember what should have been entered. We recommend a budget item for hiring and training designated data-entry personnel whose job is dedicated to timely data entry. Similarly, during heavy subject-recruitment periods, hiring and training extra personnel to assist in screening and recruitment will be well worth the added expense. Finally, during heavy periods of data analysis, hiring and training extra personnel who can assist the DMC in number crunching, writing code, and cross-checking would be another worthwhile expense that can have high pay-offs related to timely dissemination of results.

Other recommendations that may be simplistic or obvious but are essential include the opportunities for regular communication between investigators, evaluators, interventionists, and project staff. Using the example of PTClinResNet, communication strategies included monthly conference calls with the steering committee, weekly email updates about recruitment and other business as appropriate, annual reports, and annual investigator meetings to the Physical Therapy Foundation. All decisions and discussions were documented and archived for later reference as steering committee minutes, summary documents, and all emails. Lastly, for overall success, it is important to foster an attitude of flexibility and support within the scientific and clinical teams—especially when unanticipated opportunities arise that require juggling priorities (e.g., conference presentations, abstract deadlines). Respect for the cross-discipline differences that are part of the strength of any interdisciplinary collaboration is important—in the end, these diverse perspectives are what make the network team stronger. One should recruit

expert clinical scientists into the team who understand the nature of interdisciplinary collaboration and who will be invested in the goals and opportunities that a network affords. Finally, when constructing a budget for a network, consideration should be given to many of the hidden costs associated with running the network. In the case of PTClinResNet, several investigators sought out additional supplemental funds that included participating institutional support in the form of donated indirect facilities and administration costs, graduate student training grant funds, various fundraising efforts from private sources (donations), and volunteering their own personal time.

The future of PTClinResNet is still under consideration. One plan is to make the network available to other investigators who are interested in expanding the scope of their clinically related research. In this way, the network will grow in numbers of investigators but still maintain a strong core of services related to coordinating center functions. Another plan is to align the network with efforts to develop a clinical and translational sciences institute. This latter strategy would capitalize on the NIH Roadmap initiatives to foster interdisciplinary clinical research teams in rehabilitation. To a large extent, the ultimate fate of this network will be determined by the vision and value placed on interdisciplinary rehabilitation research collaborations both inside and out of academic medical centers. There has been considerable debate of late within the rehabilitation community about these issues and the need to develop research capacity in rehabilitation medicine.[37] We are hopeful that in the future there will be a broader vision for the value of interdisciplinary collaborative teams, especially for the kinds of complex problems that emerge in conditions of chronic disability.

ACKNOWLEDGMENTS

This project was supported by a grant from the Foundation for Physical Therapy to establish PTClinResNet: a clinical research network to evaluate the efficacy of physical therapist practice. Additional funding from NIDRR to Bryan Kemp, PhD, supported the STOMPS project. The authors acknowledge Jennifer Bandich, USC research administrator; Victoria Matthews, from the Foundation for Physical Therapy; Judith M. Burnfield, for design of the network figure; and the following investigators, project coordinators, intervention therapists, blinded evaluators, data-management personnel, surgeons, translators, clinics, subjects, and their families (the latter not listed):

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Recruitment: California Children's Services (Lisa Mena, MPT, Eric Lingren, MPT, and the Perez, South Bay, Miller, and Orange County Medical Treatment Units)

Corporate Donations or Discounts: Helen's Cycles, Santa Monica, Freedom Concepts, National AMBUCS, Inc., Sam's Club

Volunteers and Foundations: Caitlin Fowler, Ernie Meadows, Sidney Stern Memorial Trust, Steinmetz Foundation, Sykes Family Foundation, UCP Research and Education Foundation

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