Methods for a Multisite Randomized Trial to Investigate the Effect of Constraint-Induced Movement Therapy in Improving Upper Extremity Function among Adults Recovering from a Cerebrovascular Stroke*

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This article describes the study design, methodological considerations, and demographic characteristics of a phase III RCT to determine if 1) constraint-induced therapy (CI therapy) can be applied with therapeutic success 3 to 9 months after stroke across different sites, 2) gains that might occur persist over 2 years, 3) initial level of motor ability determines responsiveness to CI therapy, and 4) the treatment effect differs between those treated before 9 months and after 1 year. Six sites will screen and recruit poststroke survivors stratified on initial level of motor ability and after randomization allocate participants to immediate or delayed intervention. Primary outcomes include a laboratory-based measure of function (Wolf Motor Function Test [WMFT]) and a real-world participant-centered functional use measure (Motor Activity Log [MAL]). Secondary outcomes concern function, behavior, and compliance. This is the first multisite, single-blind RCT of a formal training intervention for upper extremity rehabilitation in subacute stroke in the United States.

Key Words: *RCT-rehabilitation-stroke interventions-upper extremity-motor recovery-behavior.*

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Stroke is the major cause of neurological disability in the United States. A 1998 study indicates that the number of strokes may be dramatically higher than previously estimated, reaching in excess of 730,000 every year. Moreover, more than half of these individuals are left with motor disability, and two-thirds of these survivors are still disabled 5 years later, 37% mildly so and 29% moderately or severely so.[1] Undoubtedly, the number of stroke survivors will increase greatly as the population progressively ages over the next 50 years; a recent projection is that the prevalence of stroke will more than double during this period.[2] A 2003 stroke statistics update placed the annual costs of stroke at $51.2 billion, of which $31 billion were direct medical costs and $20.2 billion were indirect costs due to lost productivity.[3] The great prevalence of stroke and its high economic costs make the reduction of stroke-related disability a national health care priority.

During the past decade, considerable effort has been made toward establishing novel approaches to overcome impairments and the compromised ability for patients to use their upper extremities to control and manipulate their environments.[4,5] Among neurorehabilitationists, this emphasis has moved away from use of specific neuromuscular reeducation techniques and toward therapies that engage the patient in some form of voluntary practice of the impaired arm and hand. One approach for which a literature is rapidly expanding is forced use or constraint-induced movement therapy (CI therapy).[6-8] Forced use emphasizes repetitive use of the impaired limb during regular activities only by means of restricting movement of the better limb.[7] CI therapy involves constraining participants to use their impaired limb on a concentrated basis by providing intensive training of impaired limb use *and* restricting movement of the better limb.[6,8-11] CI therapy is administered by a skilled practitioner using principles derived from behavioral psychology,[12] motor learning, and skill acquisition literatures.[13] Two separate detailed reviews of CI therapy have recently appeared and provide excellent backdrops for the study design and methodology described herein.[14,15]

The impetus for the Extremity Constraint-Induced Therapy Evaluation (EXCITE) trial was that up to the time of its formulation, CI therapy had been carried out successfully only in relatively small-scale, single-site studies and limited to the chronic period after stroke (see references 6 and 8 for examples). If motor deficit could be reduced earlier in the recovery period or prevented entirely, however, participants with stroke could avoid experiencing more severe impairments and longer periods of deficit than is necessary. Since EXCITE was proposed, a preliminary randomized clinical trial[16] and 2 case studies[17,18] have been published that reported that CI therapy might be helpful for patients who have recently experienced a stroke[16] or who are at a "subacute" stage[17,18] in the recovery period. The need for such studies is also important because, depending on the mechanism, the nervous system may possess greater potential for functional reorganization sooner after stroke if interventions having favorable impact can be demonstrated.

EXCITE was funded by the NIH and is the first national randomized controlled trial (RCT) to systematically examine a neurorehabilitation technique for treatment of the upper extremities among participants with stroke. It seeks to determine whether CI therapy produces more favorable functional and behavioral outcomes than usual and customary care in participants who are 3 to 9 months from stroke onset. The purpose of this article is to present the design and methodology of the RCT as well as to describe the recruitment effort and demographic characteristics of the sample recruited.

TRIAL DESIGN AND METHOD

Overview

EXCITE was designed as a multisite, prospective, randomized clinical trial. The control condition was chosen to be a delayed treatment with normal and usual care in the intervening period. Primary outcome measurements included a laboratory-based measure of upper extremity (UE) motor function (WMFT) and a participant-centered measure of real-world arm use (Motor Activity Log [MAL]) with the primary time point being at 12 months post baseline. All examiners for outcome measures were masked to treatment condition, as were raters examining videotapes. Secondary outcome measurements include variables related to function, behavior, and compliance.

At the 12-month point, the delayed treatment group received the same treatment regimen, thus providing a comparison between treatment during the subacute stage (3 to 9 months post stroke) with the chronic stage (15 to 21 months post stroke). The immediate treatment group received follow-up evaluations, thus providing tests of the persistence of the treatment effect.

Four major hypotheses were examined:

1. To determine if administering CI therapy for 2 weeks can be applied with therapeutic success to patients in the 3 to 9 month subacute post-stroke period
2. To determine whether therapeutic gains that might occur as a result of using CI therapy persist over an extended time interval
3. To test whether initial level of motor ability is a factor that determines the extent to which subacute patients with stroke are amenable to CI therapy
4. To ascertain whether the treatment effect produced by CI therapy is different among patients with subacute stroke and patients with chronic stroke

The 6 clinical sites participating in this study included Emory University (Georgia), The Ohio State University (Ohio), University of Alabama at Birmingham (UAB) (Alabama), University of Florida at Gainsville (Florida), University of Southern California (California), and University of North Carolina at Chapel Hill and Wake Forest University (North Carolina, considered 1 site).

The Data Management Center (DMC) was at Washington University (Missouri), the Training Core was at the UAB (Alabama), and the Administrative Core was at Emory University (Georgia). A Steering Committee composed of the principal investigator of each of the clinical sites and the DMC made all decisions concerning the conduct of the study. An independent Data and Safety Monitoring Committee, which periodically reviewed the progress of the study, was named. The DMC established a number of role-specific electronic mailing lists to facilitate communications among the various sites.

Inclusion and Exclusion Criteria

To capture the population that has most likely completed standard post-stroke rehabilitation, participants who are 3 to 6 months post-stroke onset from a first-time clinical cerebrovascular accident (CVA) of ischemic or hemorrhagic type at the beginning of the intervention are included. The motor criteria for participants are set for 2 groups: 1) higher and 2) lower functioning groups based on and modified from criteria set by Wolf and Binder-MacLeod[19] and Taub et al.[20] The higher functioning group must demonstrate active wrist extension of at least 20 degrees and 10 degrees of active extension of the metacarpophalangeal joints and each interphalangeal joint of all digits. The lower functioning group must demonstrate active wrist extension of no less than 10 degrees, 10 degrees of thumb abduction/extension, and at least 2 additional digits. These active movements must be performed at least 3 times in 1 minute to meet the inclusion criteria.[20] In addition to the motor criteria, participants must demonstrate adequate balance and safety while wearing the restraint. Balance criteria are that participants must be able to transfer to and from the toilet independently and safely, stand from a sitting position, and maintain standing balance independently for at least 2 minutes with or without their own UE support. To avoid any substantial structural or biomechanical restrictions to active motion, passive range of motion must be at least 90 degrees of shoulder flexion and abduction, 45 degrees of shoulder external rotation, no less than –30 degrees of elbow extension, 45 degrees of forearm supination (from neutral), 45 degrees of forearm pronation (from neutral), wrist extension to neutral, and finger extension (all digits) such that no MCP joint has greater than a 30-degree contracture.

To avoid the confounding effects of cognitive (e.g., memory deficits associated with dementia) and medical conditions, potential participants are excluded if the medical or physical screening exam reveals a score of less than 24 on the Mini Mental State Exam (MMSE), physician-determined major medical problems that would interfere with participation, a previous full-blown CVA event with clinical residual that would not meet the inclusion criteria, excessive pain in any joint or more affected extremity that could limit participation, younger than 18 years of age (adult status for informed consent), inability to meet the balance criteria, and insufficient endurance and stamina to participate in the CI therapy trial. In addition, an upper limit of performance for participation includes an average score of greater than 2.5 on the MAL Amount of Use scale at the time of the intake screen.[15] To avoid confounding effects of other intervention studies, potential participants are excluded if they are participating in other pharmacological or physical intervention studies including prior or pending participation in any form of CI therapy or have received injections of anti-spasticity drugs into UE musculature (e.g., botox) within the past 3 months or wish to have drugs injected in the foreseeable future. For practical reasons and because of the 2-year follow-up with frequent assessments (every 4 months), any eligible participants who plan to move from their local areas within 2 years are also excluded. Early experience with recruitment revealed limited availability of eligible patients within the original inclusion period of 3 to 6 months after stroke. Following consultation with the Data and Safety Monitoring Committee, the Steering Committee and DMC expanded this criterion to include participants who are up to 9 months post stroke.

Sample Size and Power

The most demanding of the primary hypotheses with respect to power is the third that requires a test of the difference in the treatment effect between the low- and high-functioning groups. A power analysis for this hypothesis was used to determine the sample size. A target of 240 participants was selected. Half would be recruited in the high-functioning group and half in the lower group. In pilot data gathered in preparation for EXCITE, an improvement was observed in the MAL of 2.2 in the high-functioning group and 1.7 in the low-functioning group. The pooled estimate of the standard deviation in these change scores (3-month

post-treatment score minus baseline) was .96. Assuming that the delayed treatment group will show an average of no change or little further improvement due to spontaneous recovery, and a similar standard deviation, and conservatively estimating that only 80% of those participants randomized (96 in each treatment group) would be available for testing at the 12-month primary endpoint testing, then the power of the test of the third hypothesis (the interaction) at a significance level of .01 would be about .85. Calculations of power for all other tests specified, other than for the third major hypothesis with respect to the WMFT outcome, have resulted in power estimates of greater than .90.

Initial Training—Academic/ Clinical Sites Assembled

In July of 1997, principal investigators from each of the participating sites attended a 5-day training program to become standardized in providing the research protocol used at the UAB. During the remainder of that year, personnel from each of the sites successfully gathered pilot data from at least 2 participants for the EXCITE grant application.

In August of 2000, after the project had been funded, all EXCITE personnel participated in a 9-day training program held by the Training Core (UAB). The program was designed to familiarize all personnel with the testing and training procedures as described in the research plan and developed at UAB.[6,9,11,12] The other purpose of this meeting was for the Steering Committee and DMC to achieve consensus on the set of revised and modified UAB testing and training procedures that were necessary for implementation of a multisite, single-blind RCT and would become the Manual of Procedures (MOP) for EXCITE. Although personnel received intensive training in the testing and treatment procedures, both were sufficiently complex as to require specific measures to ensure standardization across the EXCITE sites.

Training and Standardization

The standardization process developed by Morris and Taub requires each EXCITE project site to record a video of each tester and trainer as they perform their respective procedures using the specified protocol and camera angles. These videotapes are submitted to and rated by Training Core personnel. The rating forms have a check-off format listing critical aspects of each stage of every procedure and each item of the outcome measures as outlined in the EXCITE MOP. Before being allowed to work with participants, each tester or trainer is required to score 90% or better agreement on their performance tape with the criteria for their assigned procedures listed on the rating form. As new EXCITE personnel are hired, they are also required to meet the standardization criteria before being allowed to work with trial participants. Rechecks of the team members are conducted periodically throughout the trial. If previously standardized personnel fall below acceptable scores, they are asked to discontinue work on the project until their scores reach acceptable levels.

Site visits were also conducted during the summer of the second year of the project by either the training site coordinator or the project principal investigator. Procedures used during these visits included participant chart reviews, focus groups with research participants, and key informant interviews with EXCITE personnel. Information gathered during these visits, along with data collected with the standardization procedures, will be included in a process evaluation of the EXCITE trial.

Recruitment and Screening

Figure 1 is a standard consort flow diagram of the entire recruitment and screening process showing the actual flow of the pool of potential participants through screening and randomization. Table 1 breaks down the recruitment process by site listing the number of facilities contacted, total participant contacts, total screens, and total participants enrolled (included). Table 2 details the reasons for participant ineligibility across all the sites. The baseline demographics for the 222 participants enrolled are tabulated in Table 3.

Adverse Events

During the course of the study, significant adverse events are reported to the Administrative Core at Emory University, the DMC at Washington University, and the reporting site's institutional review board. Adverse events are defined as any unexpected change in health status, whether or not any long-term detrimental effects resulted. Events are coded based on their possible relation to the EXCITE trial. Examples of events that may be pos-

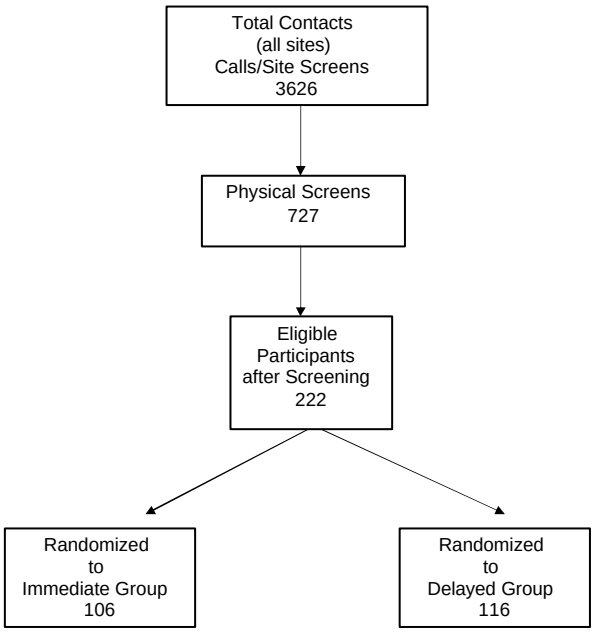

Figure 1. Flow diagram of EXCITE recruitment.

sibly related directly to the intervention include falls, musculoskeletal injuries, or medical complications, such as angina, occurring during the trial. Other unexpected events are also recorded, even if they are thought not to be related to the clinical trial, including death and unexpected illness, physician visits, and hospitalizations. Relationship to the trial is coded along a 4-point scale (*unrelated*, *possibly related*, *probably related*, *definitely related*). The severity of the event is recorded on a 4-point scale as *minor*: self-limited, no treatment required; *moderate*: treatment required but no permanent sequelae; *severe*: hospitalization required or subject left with permanent disability; *death*.

The final outcome and any necessary discussion is included on the adverse event report form and submitted electronically to the DMC. Copies of all adverse event forms are immediately distributed to all sites electronically. Any death or severe adverse event is submitted electronically to the DMC and also reported within 1 working day of learning of the event to the Administrative Core. All adverse events are appropriately reported to each local institutional review board.

Treatment Assignment

Because of concern that a simple randomization might result in noticeable imbalance with respect to important participant characteristics, an adaptive treatment assignment procedure has been adopted. Within each clinic, the balance of treatment assignments with respect to gender, premorbid handedness, side of stroke, and level of function is computed. If there is imbalance, in any of these 2-by-2 tables, the assignment is made to bring greater balance. If treatment assignments are essentially balanced, they are assigned randomly. This method is similar to the methods of Taves[21] and proceeds as follows: As each participant is presented to the Web Data Entry System (WDES) for condition assignment, the system determines the counts associated with the 4 two-by-two tables. Mathematically, the following function is then computed:

$$\sum_{k=1}^{4} \left| c_{Ijk} + 1 - c_{Djk} \right| - \left| c_{Ijk} - (c_{Djk} + 1) \right|,$$

(*Immediate* / *Delayed*)

where C_{Ijk} represents the count of immediate treatment participants in the 2-by-2 table with factor k at the participant's level of that factor. This value is summed over the 4 different factors, the discrepancy of counts made by assigning the participant to the immediate treatment condition (first term) and to the delayed treatment condition (second term). If this difference is positive, the participant is assigned to the delayed treatment condition (as a positive difference means that the immediate treatment condition would lead to more imbalance). If the difference is negative, the participant is assigned to the immediate treatment condition (as a negative difference means that the delayed treatment assignment condition would lead to more imbalance). This procedure is performed separately for each site and is very effective at maintaining balance.

Because of the logistic complexity of staffing for the immediate training condition, sites are given the option of randomizing a pair of subjects in which one of them would be assigned the immediate condition and the other the delayed condition. Information is entered into a Web-based form tied to the data entry system, and treatment assignment is implemented immediately by computer code at the DMC. A telephone backup system is available if needed.

Interventions

CI therapy, behavioral contract, daily diary, compliance. During the CI therapy intervention, the participant's less affected UE is placed in a protective safety mitt for a goal of 90% of their waking hours for a period of 14 consecutive days. This was

Table 1. Recruitment by Site

Site	Total Facilities Contacted	Total Participant Contacts	Physical Screens	Participants Included	Gender	
					Male	Female
EU	21	1138	182	40	29	11
UAB	81	469	123	39	27	12
UFL	40	498	170	39	23	16
OSU	18	619	55	29	18	11
USC	30	286	63	42	27	15
UNC/WFU	57	616	134	33	18	15
TOTAL	247	3626	727	222	142	80

EU, Emory University; UAB, University of Alabama at Birmingham; UFL, University of Florida; OSU, The Ohio State University; USC, University of Southern California; UNC, University of North Carolina; WFU, Wake Forest University.

Table 2. Summary of Ineligibility by Site: Excite Recruitment Efforts Summary—June 2000 to October 2002; Composite across Sites

Site	Reason Code												TOTAL Contacts	EXCITE Subjects
	TH	TL	TF	AP	SS	NI	TP	HS	MS	MP	SI	OP		
EU	246	155	199	24	113	37	100	5	44	31	24	119	1138	40
UAB	100	53	27	5	34	26	16	NA	NA	NA	NA	167	469	39
UFL	37	44	257	1	30	20	13	1	15	11	0	27	498	39
OSU	64	76	107	29	54	70	30	18	4	97	17	22	619	29
USC	10	34	129	3	10	16	1	0	3	11	5	22	286	42
UNC	56	36	103	3	84	64	52	6	21	39	2	35	520	18
WFU	20	10	22	6	2	2	6	NA	2	5	NA	6	96	15
TOTAL	533	408	844	71	327	235	218	30	89	194	48	398	3626	222

TH, too high on MAL (Motor Activity Log amount score); TL, too low on minimum motor criteria; TF, too far post; AP, aphasia; SS, second/multiple strokes; NI, not interested; TP, transportation problems/out-of-state inquiries; HS, hemorragic stroke (prior to changing criteria for inclusion); MS, mental status; MP, medical problems; SI, spasticity issues; OP, other problems (e.g., patient did not show for screen, did not return calls, not true cerebrovascular accident, family issues); EU, Emory University; UAB, University of Alabama at Birmingham; UFL, University of Florida; OSU, The Ohio State University; USC, University of Southern California; UNC, University of North Carolina; WF, Wake Forest; EXCITE< Extremity Constraint-Induced Therapy Evaluation.

accomplished over a 2-week period including 2 weekends for a total of 14 days at most sites except where subjects participated for 12 days with only 1 weekend included. The heavy palmer padding of the mitt prevents use of the fingers for grasping. On each of the weekdays during this period, the participant receives training in the clinical research laboratory for up to 6 hours per day. Two distinct training procedures are employed with these participants as they practice functional task activities: shaping or adaptive task practice and standard task practice. The former is a training method based on the principles of behavioral training[12,22-25] that can also be described in terms of motor learning derived from adaptive or part-task practice.[26-31]

In this approach, a motor or behavioral objective (task goal) is approached in small steps by successive approximation (i.e., parts of the task), or the task is made more difficult in accordance with a participant's motor capabilities, or the speed of performance is progressively increased. Each functional activity is practiced for a set of 10 trials, and explicit feedback is provided regarding the participant's performance with each trial. Standard task practice is less structured (for example, the tasks are not set up to be carried out as individual trials of discrete movements); it involves functionally based activities performed continuously for a period of 15 to 20 minutes (e.g., wrapping a present, writing). In successive periods of task practice, the spatial requirements of the activity or other parameters (such as duration) can be changed to require more demanding control of limb segments for task completion. Global feedback about overall performance is provided at the end of the 15 to 20–minute period. A large bank of tasks has been created for each type of training procedure. Additional tasks can be submitted and added to the bank of approved tasks only after receiving approval from the Training Core. Training tasks are selected for each participant considering 1) specific joint movements that exhibit the most pro-

Table 3. Baseline Demographic Information

Variable	Distribution
Age (y)	
Average (standard deviation)	61.7 (13.0)
Range	18.0-89.0
Gender	
Male	142 (64%)
Female	80 (36%)
Ethnicity	
African American	51 (23%)
Caucasian	147 (66%)
Hispanic	10 (5%)
Asian/Pacific Island	8 (4%)
Other	6 (3%)
Marital status	
Single	16 (7%)
Married	163 (73%)
Separated/divorced	26 (12%)
Widowed	17 (8%)
Education	
< High school	29 (13%)
High school	108 (49%)
College (graduate)	42 (19%)
College (postgraduate)	43 (19%)

nounced deficits, 2) the joint movements that trainers believe have the greatest potential for improvement, and 3) participant preference among tasks that have similar potential for producing specific improvement. Frequent rest intervals are provided through the 6-hour training day, and intensity of training (i.e., the amount of time spent on each training procedure) is documented.

Because of research personnel supervision, adherence to mitt use while in the research laboratory is usually very high. Behavioral techniques, however, are used to enhance mitt use outside of the laboratory.[6,9,11,32] These techniques include use of a behavioral contract, home diary, caregiver contract, and the daily schedule. The behavioral contract is a formal, written agreement between the interventionist and participant stating that the participant will use the weaker extremity for as many specific activities as is possible and save activities outside the laboratory. The purposes of the behavioral contract are to increase likelihood of adherence, ensure safety with mitt use, engage the participant in active problem solving, and ensure participant accountability. The behavioral contract is completed after the first day of treatment. Participants first list all activities of daily living (ADLs) typically carried out from when they awake until they go to bed. ADLs are then categorized in the contract into those to be done with 1) the more affected UE and mitt on, 2) both UEs, and 3) only the less affected UE. The time agreed on for "mitt off" activities is specified. Special attention is given to carrying out the activities safely. Activities may be added to increase UE use during down times (e.g., periodically turning pages of a magazine added during time spent watching television). ADLs may be modified to allow more-affected UE use (e.g., using a spill-proof cup while drinking liquids). The behavioral contract is signed by the interventionist, the participant, and a witness, with the formality of the process serving as a means to emphasize its importance. The behavioral contract is often modified during treatment as the participant gains new movement skills.

The home diary is kept on a daily basis; participants list their activities outside the laboratory and report if they used their more-affected UE while performing specific tasks. The home diary heightens participants' awareness of their activities and use of the more-affected UE and is thought to emphasize adherence to the behavioral contract. Discussion of the home diary also provides a structured opportunity for discussing why the weaker extremity is not used for specific activities and for problem solving on how to use it more in the future. The home diary directly supports the behavioral contract.

The caregiver contract is a formal, written agreement between the interventionist and the participant's caregiver (if there is a caregiver) that the caregiver will be present and available while the participant is wearing the mitt. The caregiver contract is completed after the terms of behavioral contract are shared with the caregiver. The caregiver contract 1) improves caregivers' understanding of the treatment program, 2) guides caregivers to assist appropriately, and 3) increases safety for the participant. The caregiver contract is signed by the interventionist, the participant, and caregiver, thereby formally emphasizing the importance of the caregiver contract.

Generally, participants arrive at the clinical laboratory for their in-laboratory activities at 9:00 AM and leave the laboratory for home at 3:00 PM. Project staff record a detailed schedule of all clinical activities carried out on each day of the intervention. This daily schedule includes time devoted to each activity listed. The schedule specifically notes the times when the restraint device is donned and removed. Also, the time and length of rest periods are recorded. Specific training activities are listed on the daily schedule. Eating lunch with the mitt on and using the more-affected UE is particularly emphasized for all participants. A daily record is kept not only of the length of time devoted to eating lunch but also what foods are eaten and how

this task is accomplished. Information recorded on the daily schedule is particularly helpful for demonstrating improvements in daily activities to the participant and thereby motivating them to try harder.

Although the use of similar behavioral techniques has been described in the physical rehabilitation literature, their use in combination and with the intensity with which they are used in this CI therapy protocol is uncommon.[32] The use of these behavioral techniques provides multiple opportunities for systematically increasing attention to more-affected UE use, promoting participants' accountability for adhering to the CI therapy protocol, and providing structured problem solving between participants and research personnel.

Finally, after completing the 14-day intervention period, participants are given a list of 8 to 10 home-practice activities and a brief description of each.[6,9,11,32] Tasks are selected that involve items typically found around the home or are easily obtainable, engage movements the participant can accomplish, and stress those movements requiring improvement. Tasks are unilateral in nature (i.e., involve use of only the more-affected UE) during the treatment period. Mitt use is discontinued after the 14-day treatment period. Participants are instructed to perform 2 to 3 of the tasks daily and spend a minimum of 30 minutes on home practice each day. They are advised to switch between tasks on different days to prevent boredom with home practice. Also, suggestions for increasing the difficulty of home-practice tasks as needed are provided. Home-practice activities are intended to be continued indefinitely.

Intervention documentation. For each task activity, the time and performance (goal achievement) characteristics are documented throughout the 6-hour intervention day. The home diary serves a similar purpose for the out-of-laboratory practice. Two different detailed recording forms are used; 1 for task practice activities (activity description, method, graded changes, date, time on task, feedback) and the other for adaptive task practice/shaping activities (time on task, activity description, each trial outcome, coaching, progression, additional information, trial-by-trial performance plot). At the end of each day, the time that the participant engaged in each type of activity (adaptive task practice/shaping and task practice) is totaled from the individual activity sheets for that day. Finally, at the end of the 14-day period, a summary form is used to tally the number of repetitions and total time on each task and over the entire 10-day in-laboratory training period. Given the variability of "time on task" that is expected across the study participants, this level of documentation should allow us to generate a dose-response curve that relates outcome to dose of therapy.

Usual and customary care. Throughout the project, participants are not discouraged from undertaking other therapeutic activities that would be considered usual and customary care. However, as these activities may have had an impact on the functional gains of the participants, an attempt is made to keep track of them. These data are obtained through participant report and collected through monthly contact phone calls by project staff and during the scheduled testing sessions every 4 months.

Primary Outcomes: UE Motor Ability and Use

Outcomes are assessed in 2 major domains: UE motor ability (laboratory-based, WMFT) and real-world UE use (structured interview, MAL). Information from these 2 domains are gathered separately.

Laboratory-based measure of UE use. This impairment-based test was developed by Wolf et al.[7] and modified by Taub and coworkers[6] to quantify motor function in stroke and traumatic brain injury patients with UE motor deficits in the range exhibited by the cohort of patients in this trial. The WMFT consists of 17 items, 2 of which involve strength measures and 15 of which involve timed performance on various tasks. Performance time (up to 120 seconds), strength (in pounds for lifting or handgrip), and quality of motor function (6-point scale of functional ability) are assessed. The WMFT contains tasks that are sequenced to progressively use more UE joints and include movements that range from simple movements, such as bringing the hand to a table top, to more complex movements that require control over all UE joints, such as turning over a series of note cards. This test was originally devised to assist clinicians in refining treatment to target specific joint-related movement limitations. The starting points and endpoints for each task are explicitly defined. On each occasion, the less impaired arm is tested first; the more-impaired arm is tested second. The former provides a point of comparison indicating how marked the initial and posttreatment motor deficits of the more-affected extremity are compared to the less-affected

arm. The time to complete each task with each UE, as well as force generated on the grip and lift strength tasks, is recorded by the tester. Functional ability is scored from videotape by the independent observers at the Training Core who are blinded to the group and treatment status of participants. The WMFT has been shown to have good clinimetric properties in the stroke population.[33,34]

Real-world arm use. The primary outcome measure in this domain is the MAL,[6,35] which is a semistructured interview during which participants are asked to rate how much (Amount of Use scale) and how well (Quality of Movement scale) they use their more-affected arm for 30 ADL/instrumental activities of daily living (IADL) items in the home over a specified period. The tasks include such activities as brushing teeth, buttoning a shirt or blouse, and eating with a fork or spoon. Information is gathered from participants about motor activity in the week prior to randomization in EXCITE, the days before and after the intervention, and at each follow-up time point (approximately every 4 months). In addition, the MAL is administered independently to an informant, who is usually a participant's primary caregiver. These records permit the participants' self-reports to be compared with less subjective accounts of their behavior. A common frame of reference for scoring the MAL across participants and measurement occasions is established by showing a videotape depicting individuals with stroke carrying out 8 of the MAL tasks at each level of performance to participants and informants prior to the initial structured interview and, as needed, on other testing dates. In contrast to the administration schedule for previous research reports, here the MAL was administered only before and after the 14-day intervention period (and at follow-up) but not daily (see Table 4).

Secondary Outcomes

Among additional tests that are administered are accelerometry,[35,36] the Actual Amount of Use Test,[20,35] and the Stroke Impact Scale.[37] Accelerometry and the Actual Amount of Use Test are, respectively, objective and observational measures of real-world UE use. The purpose of including these 2 instruments is to obtain convergent measures of more-impaired UE use, which is measured directly by the MAL. The Stroke Impact Scale provides an index of the effect of the intervention on participants' quality of life.

Accelerometry. This instrument provides a direct and objective measure of the amount of more-impaired arm movement outside the laboratory.[35,36] Immediate-treatment participants are asked to wear an accelerometer on each arm for 3 consecutive days before and after treatment and at 1-year follow-up; delayed-treatment participants are asked to wear accelerometers on a parallel schedule. Participants are instructed to take the devices off when they are sleeping or in contact with water.

The accelerometers used are wireless plastic units about the size and weight of a large wristwatch[38] that are worn proximal to the wrist on terrycloth bands. They are based on uniaxial piezoelectric crystal technology.[39] Acceleration is sampled at 10 Hz and summed over a user-specified epoch. The recording epoch in this study is 2 seconds; recording capacity is 128,000 epochs or approximately 72 hours. A "threshold-filter" is applied to the raw recordings to obtain an accurate measure of the duration of arm movement.[36] The primary summary variable is the ratio of the duration of more-impaired to less-impaired arm movement. This variable controls for changes in the overall level of activity because such changes are expected to affect recordings from the more-impaired and less-impaired arms roughly equally.[40] The accelerometer data are preprocessed by the Training Core; preprocessing involves running the data through computer programs that a) check whether the units have been worn appropriately (e.g., left arm unit actually worn on left arm) and b) discard sections of the data when the accelerometers are not being worn. Calculation of the summary variables is performed by the DMC.

Actual Amount of Use Test. The objective of this measure[20,35] is to obtain as good an index as possible of the actual amount of use of an extremity in ADL in the real-world setting by observing spontaneous use of the more impaired UE in the clinic. The participant is prompted unobtrusively to undertake 17 activities that involve UE use. (Three of the activities occur throughout testing: gesturing while talking, arm posture while walking and while standing/sitting.) The scenario for each activity does not focus attention on the affected extremity, nor is the participant aware that the test is taking place. Participants, who have previously given informed consent to be videotaped, are unaware that their performance is being recorded during testing. The quality and amount of more-impaired UE use is rated from videotape by trained, blinded observers using a 5-step Quality of Movement scale and 2-step Amount of Use scale, respectively.

Table 4. Participant-Specific Timeline for Procedures and Measurements

Preenrollment Procedures
Phone screen
Informed consent given on-site
Screen minimum motor criteria (film only if questionable)
Medical release
Medical screen exam
Schedule of availability
Randomization within 1 month of screen date (official enrollment)

Postenrollment Test and Measurement Schedule

Time Point	Test Label	Specific Tests or Procedures
Day 1	Base date	Reference date
Day 1-3	Pre1A	Base accelerometry
Day 4 (within 7 days of Accel)	Pre1T	Baseline tests (AAUT, WMFT, MAL, Caregiver MAL, Phys Exam, SIS)
Day 5-19 (within a 3-week period)	T1-T10	Constraint-induced movement therapy (CI) training (intervention group) or waiting (delayed group), compliance device recording for intervention group, daily pain & fatigue, and daily activity (intervention group)
Day 20-22	Post 1A	Post accelerometry
Day 23 (within 7 days of accelerometry)	Post 1T	Post-period tests (AAUT, WMFT, MAL, Caregiver MAL, Phys Exam)
Month 4	Month 4T	Follow-up tests (WMFT, MAL, SIS)
Month 8	Month 8T	Follow-up tests (WMFT, MAL)
Month 12 (1 y)	Pre 2A	Screen and medical screen for delayed group; accelerometry both groups (3 days)
Month 12	Pre 2T	Pretest for delayed group; follow-up for intervention group (AAUT, WMFT, MAL, Caregiver MAL, Phys Exam, SIS)
Month 12 + 14 days (within a 3-week period)	T1-T10	CI training for delayed group, compliance device recording, daily pain & fatigue, and daily activity for delayed group; waiting for original intervention group
Month 12 + 15-17 days	Post 2A	Post accelerometry (both groups)
Month 12 + 18 days (within 7 days of accelerometry)	Post 2T	Posttests for delayed group; companion tests for intervention group (AAUT, WMFT, MAL, Caregiver MAL, Phys Exam)
Month 16	Month 16T	Follow-up tests both groups (WMFT, MAL, SIS)
Month 20	Month 20T	Follow-up tests both groups (WMFT, MAL)
Month 24	Month 24T	Follow-up tests both groups (WMFT, MAL, SIS, Caregiver MAL)

MAL, Motor Activity Log; AAUT, Actual Amount of Use Test; WMFT, Wolf Motor Function Test; SIS, Stroke Impact Scale; Phys Exam, physical exam.

Additional Measures

Physical exam. The physical examination consists of physiological and anthropometric measures, passive range of motion, active range of motion, sensory and motor portions of the Fugl-Meyer test, spatial perception, spasticity, balance, and mobility/locomotor function. Specifically, the therapist examination includes measures of: passive and active UE range of motion, the UE sensory and motor portion of the Fugl-Meyer, spasticity using the modified Ashworth Scale, visual perception using a portion of the Behavioral Inattention Test and the Clock Drawing Test, and balance measured by the EPESE battery, 360-degree turn, falls frequency, and assistive devices used.

Compliance. The compliance device consists of a capacitive sensor and a timer circuit powered by a 9-volt transistor battery. These 2 components are inserted into the protective safety mitt worn by participants during the 14-day treatment period. The compliance device is used to measure compliance with the requirement of CI therapy that the participant wear the mitt to limit use of the less-affected hand for a target of 90% of waking hours.

The sensor (approximately 6 by 15 by 0.5 cm) is attached to the mitt and is situated just under the palm of the participant's hand. The battery, circuit board, and display are housed in a plastic enclosure (approximately 6 by 9 by 2 cm) attached to the mitt at the subject's wrist. The circuitry, battery, and sensor together weigh about 4 ounces. The

compliance device uses very low power, most of which is consumed by the lead crystal display and timer circuit. When a participant's hand is placed in the mitt, a conducting path is established between 2 parts of the sensor, and the timer is activated. When the mitt is removed, the conducting path is broken and the timer stops until the mitt is donned again. The compliance device is worn during the 14-day intervention period. During weekdays, the CI trainer reads and records the display in the morning when the participant arrives at the training site. The counter is read and recorded again at the end of each intervention day and reset prior to the participant's departure from the training site that day. Participants return the mitt and compliance device to the site personnel after the 14-day treatment period.

Dropouts

Following the intent-to-treat principle, even those participants who were unable to complete all treatment sessions are still encouraged to attend each scheduled assessment. Reasons for withdrawals are documented.

Baseline, Post-Immediate, and Quarterly Evaluations

Table 4 outlines the timeline for baseline, pre- and posttreatment/control period, quarterly, and crossover evaluations. Not all outcomes are evaluated at each evaluation visit. Primary outcomes (WMFT, MAL) are evaluated at pre 1, post 1, and every 4 months (month 4, month 8, month 12/pre 2, post 2, month 16, month 20, and month 24). The crossover point is designated as pre 2 and occurs at month 12 from the baseline date.

Single-Blinding Considerations

Because this is a physical intervention and participants know if they are not receiving training (i.e., randomized to the delayed group) or are receiving it (i.e., randomized to the immediate group or crossed over to CI therapy), only the evaluator (i.e., person administering the outcome tests) can be kept blinded to treatment condition (i.e., single blind). This requirement can be accomplished for the baseline/pre-1 evaluation with relative ease if the participants are randomized but not informed regarding group assignment until after the pre-1 evaluation is complete. At all subsequent evaluation points, participants and caregivers are briefed and reminded of the importance of keeping the evaluator blinded. Letters are sent prior to all subsequent evaluations that include reminders and examples to facilitate the blinding process. In all cases, personnel who carry out training are different from those who carry out evaluation testing. To further ensure blinding, the physical location of the training site is separate from the testing site at each center to reduce the possibility of accidental encounters between evaluator and participant during the training periods.

Plans for Retention and Compliance

To encourage continued participation of all participants between testing dates, each person enrolled is contacted monthly by phone; this contact serves to maintain a positive relationship between the project staff and the participant. In addition, birthday cards, cards for other special occasions (e.g., Christmas), and a monthly newsletter, developed by the project staff, are mailed to the participants. Other methods of encouragement include giving participants project items (t-shirts, coffee cups, Post-it notes with the EXCITE logo) in recognition of their participation and completion at each time point.

Data Entry and Management

Development of the Manual of Procedures (MOP). A MOP for the EXCITE trial was customized and revised from materials prepared for use in the project's training workshop. All methods are detailed specifically for EXCITE. The MOP has been made available to all investigators and staff in hard copy, and an electronic version is stored on the study's website (www.excite.wustl. edu). The electronic version is updated as needed during the conduct of the study.

Electronic data entry. Data entry for the EXCITE trial is performed using the WDES.[41,42] This is a SAS/IntrNet®-based thin-client system for data editing. At each site, the system is accessed with an Internet browser (Netscape Navigator version 6.2 or higher; Internet Explorer version 5.2 or higher). Using the browser, an HTML page on the server at the DMC is accessed using a URL. This is termed the "on-ramp" page and provides access to the dif-

ferent forms for the project. For the EXCITE project, 23 different forms are supported by the WDES.

The process of accessing and editing information occurs in the following manner. First, the user logs in by accessing the on-ramp page. At this time, the *htaccess* protocol (i.e., takes as argument a string designating a file that is to be used for login-password verification) requests that the user name and password be supplied. Internally, the name information is stored and is made available to the browser. The user then selects a form for data entry or data editing. At that point, the WDES generates the form dynamically. As a part of this process, the system incorporates a "select" list for only the participants at the user's site, and thus the users at one site are not able to access the records of participants from any other location. This goal is accomplished by referring to the user name. The dynamically generated page is returned to the user, and the user may then select a participant for editing, add a new data observation to the data set, or perform other functions. When new data are added to the system, the user begins by entering the data into the form at that time. For editing, the process begins by sending a request using the WDES to the DMC and returning the data in editable form to the user. After data are entered into the form or modified from existing values, the user initiates the return of the form to the server. JavaScript code is used to verify and check the data. Some variables are required items, ranges for some variables are checked, and some forms involve somewhat complex dependency between items. These procedures enhance the accuracy and validity of the data submitted. After the data have passed all JavaScript screening tests, they are passed to the server and directly entered into the specific SAS data set related to the form; each form is associated with a single data set. The transaction is completed by returning a "receipt" to the user, which involves a listing of the data as stored by the WDES (in the same format as the original form) to the user; users are encouraged to print these for retention in the participant file.

On the server, the data from each form are stored in a separate data set. The data are backed up daily to a separate data set for each day of the month, and monthly backups are maintained as well. Periodically, the backup values are written to CD, and the CD is stored in several places (both on- and off-site). The data and the WDES files are separately backed up. Each transaction is stored in a SAS-system audit trail. The SAS system audit trails maintain all records as added and before and after modification. The SAS audit trails are lost when the data set is sorted, and so data sets within the WDES are never sorted. All changes to the data sets are performed using the MODIFY statement, which is an in-place tool for data modification (i.e., data are changed in place rather than the file being rewritten). To ensure that audit trails are maintained if the data set is rewritten, the audit trail is itself backed up to a separate audit trail backup data set. Separate backups are performed by the server on a daily, weekly, monthly, and quarterly basis. Unblinding procedures are not needed since the trial is only blinded to the assessors.

Data Analysis

All statistical analyses are conducted by DMC personnel using standard statistical software (primarily SAS, SAS Institute, Cary, NC). In all cases, the technical assumptions required for the statistical models (e.g., normal distributions of error terms) are compared to the actual data to determine their reasonableness prior to the acceptance of the statistical analyses. All analyses are checked by a different DMC statistician from the one performing the analyses. The intent-to-treat principle is employed in all primary analyses.

Hypothesis 1. To determine if CI therapy for 2 weeks can be applied with therapeutic success to patients in the 3 to 9 month subacute post-stroke period.

Operational definition: participants will show significantly greater improvement in real-world outcome (MAL) and on laboratory motor test measures (WMFT) than those patients randomized to usual and customary care after treatment and at 1- and 2-year follow-up time points. This hypothesis will be tested for each of the primary endpoint variables (MAL and WMFT scores at 12 months) with a 2 by 2 analysis of covariance with treatment group (CI vs. standard care) and functional level (low vs. high) as the 2 factors and baseline value of the variable as the covariate. The primary test of the treatment will be a test of the treatment effect *within each level of functioning*. An interaction between the slope for the baseline covariate and functional level will be tested and, if appropriate, made to fit a model with separate slopes. The tests within each level of functioning will be at .005 to achieve an overall analysis significance of .01 for each endpoint.

For secondary analyses of this hypothesis, other endpoints will be analyzed in a manner similar to those for the primary endpoints. These secondary endpoints include Actual Amount of Use Test,

accelerometry, and the Stroke Impact Scale. In addition, analyses that include race and gender will be conducted to verify that the results will generalize to women and minority subjects.

Hypothesis 2. To determine whether therapeutic gains that might occur as a result of using CI therapy persist over an extended time interval.

Operational definition: analyses for this hypothesis will be based on a repeated measures ANOVA (univariate approach with Proc MIXED of SAS) that will allow both comparisons of the treatment group effect at each time point (posttreatment, 4 and 8 months postrandomization) and comparisons between time points to evaluate the persistence (decay) of the treatment effect. These time points include the 16-, 20- and 24-month evaluations for the immediate treatment group. Secondary analyses of this hypothesis will include parallel analyses of secondary endpoints as identified in the analyses for Hypothesis 1.

Hypothesis 3. To test whether initial level of motor ability is a factor that determines the extent to which subacute patients with stroke are amenable to CI therapy.

Operational definition: there will be an interaction between pretreatment functioning (as measured by the high/low functioning grouping) and the magnitude of the treatment effect. This will be conducted by augmenting the models used in Specific Aim 2. Secondary analyses will include parallel analyses of secondary endpoints as identified in the analyses for Hypothesis 1.

Hypothesis 4. To ascertain whether the treatment effect produced by CI therapy is different among patients with subacute stroke and patients with chronic stroke.

Operational definition: there will be no significant difference in the treatment effect for the subacute and the chronic (crossed-over) patients treated in this project.

This will be evaluated by statistical models identical to those described above, except that for the delayed-treatment group, the 12-month evaluation values will be used as the baseline, and the post-T2-, 16-, 20- and 24-month values will be used as the post-T1-, 4-, 8- and 12-month evaluations. This approach provides a comparison in which the grouping is under randomization, although the delayed-treatment group will have had prior testing experiences and there will be a differential attrition between the 2 groups.

DISCUSSION

Multisite clinical trials research in neurorehabilitation is a comparatively new focus for clinician-scientists in rehabilitation fields such as physical therapy, physical medicine, occupational therapy, and rehabilitation psychology.[43]

The process of determining efficacy and effectiveness for any new therapy (pharmacologic or neurorehabilitation) proceeds through the scientific experimental development process from an initial discovery phase to a preclinical phase and finally phase I, II, III, and IV clinical trials. EXCITE is classified as a phase III, which seeks to demonstrate efficacy and effectiveness of CI therapy in a large-scale, well-controlled, randomized and multisite clinical trial. The EXCITE investigators considered the degree to which the animal research from a deafferented primate model[44] could be, or for that matter should be, translated to a phase III RCT in humans at the subacute phase after stroke. Although considerable translation in this area has been undertaken thus far,[14,15(for review)] many factors such as the optimal duration, specific training methods, intensity of training, progression techniques, inclusion criteria, optimal timing after stroke, and so forth have not been exposed systematically to the experimental development process.

Interventions in neurorehabilitation aimed at reducing the impairments associated with the disabling consequences of stroke-hemiparesis, especially those that target manual skills and UE function, require consideration of a minimal clinically important difference for evaluation of efficacy and effectiveness. Although there is no universal approach to the determination of a minimal clinically important difference, the factors that should be considered include disease-specific and relevant outcomes, chronic versus acute conditions, and baseline or start point characteristics. To this end, the exact design and methods chosen for the EXCITE phase III RCT were determined through a consensus process using a combination of best judgment, prior experience, expertise of the EXCITE investigators, and the literature. For example, one critical inclusion criterion requires demonstration of some degree of voluntary extension (opposite gravity) movement in the wrist and fingers. This inclusion criterion most likely excludes a significant proportion of the stroke population from this intervention (see reference 14 for recent discussion). However, a focused approach that includes a carefully reasoned set of inclusion crite-

ria is essential for interpretable and conclusive results when determining the effectiveness of a therapeutic intervention (see reference 45 for a recent commentary).

Because EXCITE is 1 of only 2 multisite clinical trials in neurorehabilitation in the United States to date, EXCITE investigators needed to develop several new methods to overcome problems specific to conducting multisite, blinded, randomized trials of rehabilitation interventions. The primary methodological innovation is the procedure for standardizing the administration of the intervention across sites. The process of standardizing a complex intervention forces the investigative team to identify the critical ingredients of the intervention. Complex interventions are built up from a number of components that act both independently and interdependently. Components usually include behaviors, parameters of behaviors (e.g., frequency, timing, intensity), and methods of organizing and delivering those behaviors (e.g., type(s) of practitioner, setting, and location). Unlike pharmacological interventions, in which subject participation is relatively passive and administration of treatment is relatively simple, physical interventions involve substantial active participation on the part of subjects and complex behaviors on the part of therapists. Precisely defining the "active ingredients" of a complex intervention is not trivial, yet the scientific rigor of a multisite RCT demands such procedures. The standardization procedure, which involves video recording of trainer and tester performance at regular intervals and review by a central training core, appears to be a successful means of ensuring fidelity in the administration of the treatment and testing techniques across sites and might serve as a model for standardizing the delivery of treatments in future multisite trials. Other methodological contributions of the EXCITE trial include the development of guidelines for specifying rehabilitation interventions; methods for reliable, blinded scoring of large numbers of laboratory motor tests; and automated techniques for reliably processing large volumes of accelerometer data. In addition, the WDES used in the trial represents a state-of-the-art approach toward data management in a multisite clinical trial.

There are some limitations in the study design. As noted, physical rehabilitation involves active participation on the part of patients. Because controlling factors such as initial level of motor ability, type of sensory and/or motor deficit, patient motivation, and family support that determine patient participation are difficult to specify, we chose to record variation in treatment participation (e.g., duration of training activities) and compliance (e.g., time mitt worn) rather than to control these variables experimentally. Another limitation is that subjects are not blinded to group assignment. This represents a particular challenge for rehabilitation given the difficulty of designing credible sham interventions. Partly because of budgetary considerations, we have chosen a standard and customary care control group. This design will permit us to compare the effectiveness of CI therapy to existing clinical care; however, it will not allow comparison relative to a placebo effect. Not evaluating the cost-effectiveness of this study compromises its external validity. These measures are not taken largely due to budgetary considerations. Rehabilitation funding agencies may want to consider increasing the amount of money available to fund national clinical trials to permit evaluation of these 2 increasingly important questions.

The EXCITE Steering Committee considers that the design and implementation of this RCT provides a valid example of the application of the principles of hypothesis-driven translational research in neurorehabilitation, and operational methods to overcome the challenges (e.g., standardization of treatment) and barriers (e.g., evaluator blinding) unique to clinical trials in physical therapy rehabilitation (see recent editorial[46]). Currently, there are only 2 large-scale, well-defined, randomized clinical trials for neurological rehabilitation—EXCITE and SCILT (Spinal Cord Injury Locomotor Training). Regardless of the findings of either of these recent efforts, the design and implementation of such pioneering trials opens the door for planning other multicenter trials in neurorehabilitation.

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