The EXtremity Constraint-Induced Therapy Evaluation

The EXCITE Randomized Clinical Trial

Funded by: The National Center for Medical Rehabilitation Research (NCMRR) of the National Institute for Child Health and Human Development and NINDS (NIH)

The Investigator Team

- **Co Principal Investigators**
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- **Director, Data Management Center**
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The Investigator Team

- **Site Principal Investigators**
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  - **Carol Giuliani**, Ph.D., P.T. (University of North Carolina) and **David Good**, MD (Wake Forest University, North Carolina)
  - **Gitendra Uswatte,** Ph.D. and **Edward Taub,** Ph.D. (University of Alabama at Birmingham)
  - **Deborah Nichols**, Ph.D., P.T. (The Ohio State University)

Constraint Induced Movement Therapy (Forced Use)

- **Collaborators**
  - Brigitte Jann, M.D.
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- **Graduate Students**
  - Carol Ostendorf, M.Ms.P.T.
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  - Amy Piancetino, M.P.T.
  - Marcy Swanson, DPT
  - Jill McJunkin, DPT

The EXCITE Trial: Historical Perspectives

- February 1996: Taub and Wolf make presentation to American Physical Therapy Association (APTA) Neurology Section
- 1996 periodic conference calls
- February 1997: Wolf asks Neurology Section for $6000
- May 1997: planning meeting at Emory
- **June 1997: Wolf and Miller meet with NCMRR**
- July 1997 standardization of Constraint-Induced Therapy (CIT) application at UAB

The EXCITE Trial: Historical Perspectives

- Letter of Intent
  - Overview
  - Timeline
  - Budgets
- Permission/Approval
- Keeping costs down – agreed to maximum

Establishing a Clinical Research Agenda: Basis for Seeking Funding

- I. Concept
  - A. Original or response to Request for Application (RFA), (Line 2)
    - "helping the CSR"
  - B. Personnel
    - Track record
    - Past productivity
    - Past training including post-doc experience

Establishing a Clinical Research Agenda: Basis for Seeking Funding

- Ia. Collaborations/referrals
  - A. Resource personnel
  - B. Clinical research experience
    - Relevance to specific aims
  - C. Defining the collaboration
    - Establishing fiscal responsibilities/commitments
    - Resources and environment
    - Teamwork and output information dissemination

Establishing a Clinical Research Agenda: Basis for Seeking Funding

II. DESIGNING PROTOCOLS

- Don't be afraid to ask.....
  - colleagues, biostatisticians
  - non-academics
- What will set you apart?; that is: what is **unique** or **innovative** about your idea and should that uniqueness be noted in your protocol?
- To avoid pitfalls:
  - Think!!!!
  - Be critical of input!
  - Once completed – start over!
  - Repeat and refine

Establishing a Clinical Research Agenda: Basis for Seeking Funding

III. The "Unknowns"

- A. Biosketch – selling job!
- B. Appendices and support
- C. THINK AS A REVIEWER, NOT AS AN APPLICANT
  - 10-14 REVISIONS
- D. If it ain't ready, don't' submit!
  - Don't wait until the last minute (e.g. our next TC grant)
- E. Persistence
- F. Talk with project officer – your friend!

The EXCITE Trial: Historical Perspectives

- August-December 1997: pilot data acquisition from 14 subjects across 7 sites
- January 1998 - February 1998: analyze data (Taub and Miller), write narrative (Wolf and Taub) {statistical section: Miller; site specific information: site PIs}
- late February 1998: decide grant not ready for March 1 deadline

The EXCITE Trial: Historical Perspective

- June 1, 1998: submit grant
- November 1998: telephone conference call
- December 31, 1998: receive grant reviews
- January - February 1999: Wolf, Taub, and Miller respond to critiques, rewrite, and get updated information from site PIs
- March 1, 1999: grant resubmitted
- May 5, 1999: reverse site visit conf. call

Recruitment Summary

EXCITE RECRUITMENT EFFORTS SUMMARY. JUNE 2000-2002 2

COMPOSITE ACROSS SITES

Site	TH	TL	TF	AP	SS	NI	TP	HS	MS	MP	SI	OP	EXCITE	
EU	245	155	199	24	113	37	100	5	44	31	24	120	40	
UAB	100	53	27	5	34	28	16					169	39	
UFL	37	44	257	1	30	20	13	1	15	11	0	30	39	
OSU	84	76	107	29	54	70	30	18	4	97	17	24	29	
USC	10	34	129	3	10	16	1	0	3	11	5	22	42	
UNC	56	38	103	3	84	64	52	6	21	39	2	36	18	
WF	20	10	22	6	2	2	8		2	5		6	15	
TOTAL	533	408	844	71	327	235	218	30	89	194	48	407	222	

TH: too high (533)
TL: too low (408)
TF: too far post injury (844)
AP: aphasia (71)
SS: second/multiple strokes (327)
NI: not interested (235)
TP: transport problems (218)
HS: hemorrhagic (30)
MS: mental status (89)
MP: medical problems (194)
SI: spasticity excessive (48)
OP: other problems (no show, not stroke) (407)

EXCITE: LESSONS LEARNED

- **Coordination**
  - Thankless and time consuming
  - Strong oversight
- **Recruitment**
  - Time consuming
  - Rehab versus pharmacological clinical trials
  - Catastrophic injury versus non-catastrophic
  - Transportation

EXCITE: LESSONS LEARNED

- **Psychosocial**
  - Acute versus sub-acute versus chronic
  - Family dynamics
  - Cultural perspectives
- **Administrative**
  - Manual of Procedures (MOP)
    - Adherence to procedures
  - Fore-play or is it fore-planning (perhaps both?)
- **Adverse events monitoring and reporting**
- **Data Safety and Monitoring Board**
  - Advise and guidance
- **Information and dissemination**

Future Research Perspectives
www.excite.emory.edu

COMPONENTS:

A. **Interventional**
   A. Physical (S. Wolf et al) [NCMRR, NIH: HD/NS 37606]
   B. Behavioral
      A. Caregiver (P. Clark et al) [NIH: NR07612]
      B. Clinician
   C. Virtual Environment (New Jersey)
      A. Neuroimaging (Butler)
   D. Visual imagery (Butler) [NIH, R21 pending)

B. **Mechanistic**
   A. Neuroimaging/TMS (EXCITE) (D. Good et al) [NIH: HD40984] (Emory: K. Sathian, S. Wolf, A. Butler, H. Mao)
   B. Biomechanics (EXCITE) (J. Alberts) (VA Merit Review, NIH R21, pending)
   C. Molecular – Biomarkers as precursors to neuronal reorganization

Constraint Induced Movement Therapy (EXCITE Trial)

- Minimal Motor Criteria
  - Higher Functioning
    - $>20^0$ wrist extension; $>10^0$ extension of all digits
  - Lower Functioning
    - $>10^0$ wrist extension; . 10^0 thumb and two other digits
  - Performance x3 in 1 minute

The EXCITE Trial: Inclusion/Exclusion Criteria

INCLUSION:

- Minimal motor criteria: higher and lower functioning
- Willingness to participate; signed informed consent
- Not excluded if have somatosensory deficits
- Any type of previous rehab interventions
- < 2.5 Motor activity log (MAL)

The EXCITE Trial: Inclusion/Exclusion Criteria

EXCLUSION:

- Under the age of 18
- Terminal illnesses
- Intent to move or relocate too far away
- Present pharmacological therapy
- Intended pharmacological therapy
- Not meet minimal motor criteria
- Extreme aphasia or mental incompetence

The EXCITE Trial: Overview

- Primary outcome measures (developed by Taub et al. at UAB):
  - Modification of the Emory Motor Function Test (Wolf Motor Function Test)
  - Motor Activity Log (MAL)

The EXCITE Trial: Primary Outcome Measures

Wolf Motor Function Test (WMFT)

impaired-based, laboratory and real-world measures designed to examine segmental and inter-segmental movements

Motor Activity Log (MAL)

30 real world measures typically performed in the home environment

The EXCITE Trial: Overview (continued)

Secondary outcome measures:

- Actual Amount of Use Test (AAUT) {Taub et al.}: real-world measure of spontaneous use of limb (videotaped)
- Accelerometry:
- Stroke Impact Scale {Duncan et al}: 64 items, 8 domains: strength, hand function, combined Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs), mobility, memory, communications, emotion, socialization

The EXCITE Trial: Pilot Data

- 9 higher, 5 lower level functioning stroke subjects
- MAL Dose-response curves over 10 days of treatment (repeated measures ANOVA with functioning level as between subject variable and Rx day as within subject variable)
  - Functioning levels and treatment day were significant effects but no interaction (similar shaped curves with rate of change showing negative acceleration)
  - Persistence in scores at 3 month follow -up
- Caregiver responses in parallel

The EXCITE Trial: Essential Considerations

- Blinded, cross-over trial
- N = 240 sub-acute (3-6 month post-stroke subjects) across 6 sites (40 per site)
- Attempts at equal distribution of higher and lower functioning subjects
- Control group: usual and customary care

The EXCITE Trial: The Intervention

- Wearing hand splint - no thumb opposition
  - 90% of waking hours, 6 hrs/day (interventionist), 14 consecutive days
  - Splint off: water based functions, naps or agreed to circumstances
- Mass Practice of Functional Activities
  - Appropriate sequencing of task and components

The EXCITE Trial: Specific Aims

Specific Aim 1:

- Can a 2-week Constraint Induced (CI) Therapy program be applied successfully to patients with sub-acute stroke in multiple settings?
  - Between subject factors (functioning level and group assignment)
  - Within subject factor (time: 4, 8 and 12 months)
- Major point: Test of differences between groups at 12 months *within* each functioning level (higher/lower)
- Secondary analysis: Rx x time interaction: time course over the first year post-Rx is same between groups

The EXCITE Trial: Specific Aims

Specific Aim 2:

- Do the therapeutic gains achieved through CI therapy persist over time? (12-24 months)
  - Secondary analyses: (time dependent covariates: new stroke events; general physical ability; as in Specific Aim 1)

The EXCITE Trial: Specific Aims

Specific Aim 3:

- Does the initial level of motor ability (higher/lower functioning) determine the extent to which sub-acute stroke patients improve with CI Therapy?
  - *Between* levels of functioning analyses

The EXCITE Trial: Specific Aims

Specific Aim 4:

- Is the magnitude of response to CI Therapy different among patients with sub-acute stroke and chronic stroke?
  - 3-6 months versus 15-18 months post-stroke
  - Makes use of control group that has been formally randomized
  - Compares BL, 4, 8, 12-month MAL and WMFT scores to 12, 16, 20, 24 month scores for delayed RX group functioning analyses