PI: **DUNCAN, BURRIS R**	Title: Intense physiotherapies to improve function in young children with cerebral palsy	
Received: 06/04/2013	FOA: PA11-260	Council: 01/2014
Competition ID: ADOBE-FORMS-B2	FOA Title: RESEARCH PROJECT GRANT (PARENT R01)	
1 R01 HD079498-01	Dual:	Accession Number: 3592232
IPF: 490201	Organization: UNIVERSITY OF ARIZONA	
Former Number:	Department: Public Health	
IRG/SRG: MRS	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 357,980 Year 2: 458,313 Year 3: 458,313 Year 4: 474,748 Year 5: 386,388	Animals: N Humans: Y Clinical Trial: Y Current HS Code: 30 HESC: N	New Investigator: Y Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Burris Duncan M.D.	Arizona Board of Regents, University of Arizona	PD/PI
Chengcheng Hu Ph.D	Arizona Board of Regents, University of Arizona	Other (Specify)-Biostatistician
Theodore Trouard Ph.D	Arizona Board of Regents	Co-Investigator
Jorge Arango M.D.	Phonenix Children's Hospital	MPI
Ewa Brandys M.D.	Phoenix Children's Hospital	Co-Investigator

Appendices

Appendix1gmfcsinstructions,Appendix11bi weeklyphoneinterview,Appendix2gmfm,Appendix3gmfmscoresheet,Appendix4pedi,Appendix9bi weeklyphoneinterview,Appendix6dailytreamtentform,Appendix7ptformsgroups1and2,Appendix8otformsgroups1and2,Appendix0tableofcontent

OMB Number: 4040-0001
Expiration Date: 06/30/2011

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE: | **State Application Identifier:**

1. * TYPE OF SUBMISSION
☐ Pre-application ☐ Application ☒ Changed/Corrected Application

4. a. Federal Identifier: Grant11410563

b. Agency Routing Identifier:

2. DATE SUBMITTED: | **Applicant Identifier:**

5. APPLICANT INFORMATION

*** Organizational DUNS:** 806345617

* Legal Name: Arizona Board of Regents, University of Arizona

Department: | Division:

* Street1: P.O. Box 210158

Street2:

* City: Tucson | County / Parish:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * ZIP / Postal Code: 85721-9158

Person to be contacted on matters involving this application

Prefix: | * First Name: Sherry | Middle Name: L.

* Last Name: Esham | Suffix:

* Phone Number: 520-626-6000 | Fax Number: 520-626-4137

Email: Sponsor@email.arizona.edu

6. * EMPLOYER IDENTIFICATION *(EIN) or (TIN):* 1742652689A1

7. * TYPE OF APPLICANT: H: Public/State Controlled Institution of Higher Education

Other (Specify):

Small Business Organization Type ☐ Women Owned ☐ Socially and Economically Disadvantaged

8. * TYPE OF APPLICATION:
☒ New ☐ Resubmission
☐ Renewal ☐ Continuation ☐ Revision

If Revision, mark appropriate box(es).
☐ A. Increase Award ☐ B. Decrease Award ☐ C. Increase Duration ☐ D. Decrease Duration
☐ E. Other (specify):

* Is this application being submitted to other agencies? Yes ☐ No ☒ What other Agencies?

9. * NAME OF FEDERAL AGENCY: National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:

TITLE:

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:
Intense physiotherapies to improve function in young children with cerebral palsy.

12. PROPOSED PROJECT:
* Start Date: 04/01/2014 | * Ending Date: 03/31/2019

*** 13. CONGRESSIONAL DISTRICT OF APPLICANT:** AZ-003

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: | * First Name: Burris | Middle Name: R.

* Last Name: Duncan | Suffix: M.D.

Position/Title: Professor Emeritus

* Organization Name: Arizona Board of Regents, University of Arizona

Department: Public Health | Division: Health Promotion Sciences

* Street1: 1295 N. Martin Avenue, Building 202A

Street2:

* City: Tucson | County / Parish: Pima

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * ZIP / Postal Code: 85724-5163

* Phone Number: 520-907-7865 | Fax Number: 520-626-6093

* Email: bduncan@peds.arizona.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested	2,695,368.00
b. Total Non-Federal Funds	0.00
c. Total Federal & Non-Federal Funds	2,695,368.00
d. Estimated Program Income	0.00

16. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ☐ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ☒ PROGRAM IS NOT COVERED BY E.O. 12372; OR

☐ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious. or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

☒ *** I agree**

**** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.***

18. SFLLL or other Explanatory Documentation

Add Attachment | Delete Attachment | View Attachment

19. Authorized Representative

Prefix: * First Name: Leslie Middle Name: P.

* Last Name: Tolbert Suffix:

* Position/Title: Vice President for Research

* Organization: Arizona Board of Regents, University of Arizona

Department: Division:

* Street1: P.O. Box 210158

Street2:

* City: Tucson County / Parish: Pima

* State: AZ: Arizona Province:

* Country: USA: UNITED STATES * ZIP / Postal Code: 85721-0158

* Phone Number: 520-626-6000 Fax Number: 520-626-4137

* Email: sponsor@email.arizona.edu

*** Signature of Authorized Representative**: Mary Gerrow

*** Date Signed**: 06/04/2013

20. Pre-application

Add Attachment | Delete Attachment | View Attachment

424 R&R and PHS-398 Specific Table Of Contents

Appendix

Number of Attachments in Appendix: 10

OMB Number: 4040-0010
Expiration Date: 08/31/2011

Project/Performance Site Location(s)

Project/Performance Site Primary Location ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Arizona Board of Regents. University of Arizona
DUNS Number: 8063456170000
* Street1: 1295 N. Martin Avenue
Street2:
* City: Tucson County: Pima
* State: AZ: Arizona
Province:
* Country: USA: UNITED STATES
* ZIP / Postal Code: 95724-5210 * Project/ Performance Site Congressional District: AZ-003

Project/Performance Site Location 1 ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Tucson Medical Center
DUNS Number:
* Street1: 5301 E. Grant Road
Street2: Palo Verde Building
* City: Tucson County: Pima
* State: AZ: Arizona
Province:
* Country: USA: UNITED STATES
* ZIP / Postal Code: 85712-2805 * Project/ Performance Site Congressional District: AZ-003

Project/Performance Site Location a ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Phoenix Children's Hospital - Barrow Neurological Institute
DUNS Number:
* Street1: 1919 East Thomas Road
Street2:
* City: Phoenix County: Maricopa
* State: AZ: Arizona
Province:
* Country: USA: UNITED STATES
* ZIP / Postal Code: 85016-7710 * Project/ Performance Site Congressional District: AZ-007

Performance Sites

Additional Location(s) Add Attachment | Delete Attachment | View Attachment

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? ☒ Yes ☐ No

1.a If YES to Human Subjects

Is the Project Exempt from Federal regulations? ☐ Yes ☒ No

If yes, check appropriate exemption number. ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

If no, is the IRB review Pending? ☒ Yes ☐ No

IRB Approval Date:

Human Subject Assurance Number: 00004218

2. * Are Vertebrate Animals Used? ☐ Yes ☒ No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ☐ Yes ☐ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. * Is proprietary/privileged information included in the application? ☐ Yes ☒ No

4.a. * Does this project have an actual or potential impact on the environment? ☐ Yes ☒ No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ☐ Yes ☐ No

4.d. If yes, please explain:

5. * Is the research performance site designated, or eligible to be designated, as a historic place? ☐ Yes ☒ No

5.a. If yes, please explain:

6. * Does this project involve activities outside of the United States or partnerships with international collaborators? ☐ Yes ☒ No

6.a. If yes, identify countries:

6.b. Optional Explanation:

7. * Project Summary/Abstract 1234-Summary.pdf Add Attachment Delete Attachment View Attachment

8. * Project Narrative 1235-Narrative.pdf Add Attachment Delete Attachment View Attachment

9. Bibliography & References Cited 1236-References.pdf Add Attachment Delete Attachment View Attachment

10. Facilities & Other Resources 1237-Resources.pdf Add Attachment Delete Attachment View Attachment

11. Equipment Add Attachment Delete Attachment View Attachment

12. Other Attachments Add Attachments Delete Attachments View Attachments ☐

Intense physiotherapies to improve function in young children with cerebral palsy

4.2.1 Summary:

Cerebral palsy (CP) is a disorder of movement and posture caused by an injury to the central nervous system when the brain is most rapidly developing. The causes for the injuries to the brain are numerous and the degree of severity is large. The injuries can occur prior to birth, during the birth process, or within the first few months of life. Whereas the central nervous system injury is non-progressive, the motor dysfunction is often progressive. It can involve one or all four extremities but most often affects the legs, making walking difficult or impossible. The level of severity depends on the extent of the injury and can be quite mild or so severe the child is dependent on others for all his/her care. There is no known cure for CP but the brain can be reprogramed. Non-damaged neurons can be recruited to replace damaged neurons and some function can be recovered. Because of the lower myelin content and elevated concentrations of trophic factors in the young brain, releasing the capacity of neuroplasticity is greatest when the child is young. Reprograming is most likely to be accomplished with repetitive, active, task-oriented rehabilitation. The proposed double arm, randomized clinical trial will enroll 110 children ages 12 to 36 months. Group 1 will receive an intense series of physical and occupation therapies 5 times each week for 12 weeks followed by the current standard of care (SOC), the same therapies once each week for 36 weeks. Group 2 will start with the SOC for the first 36 weeks and then receive the intense series for 12 weeks. Evaluations will be done at baseline and every 12 weeks thereafter. The primary outcome measure is the change in scores on the Gross Motor Function Measure-66 (GMFM-66) from baseline to 12 weeks. Secondary outcome measures are a change in the scores on the Pediatric Evaluation Disability Inventory (PEDI) after 12 weeks, a change in the GMFM-66 and PEDI scores after 36 weeks, and after 48 weeks on the assigned therapies. Regression analysis from history, physical examination data, and MRI interpretation will be used to develop a profile of children who are most likely to benefit from the intens therapeutic approach. An exploratory aim will use diffusion tensor imagining comparing changes in neuroanatomy at 36 weeks on a subset of 20 children, 10 who had been randomized to each group. Children in this subset will be ones who were born prematurely and where there was injury to the motor neurons located in the periventricular area (periventricular leukomalacia), those neurons that are responsible for walking.

Relevance

Cerebral palsy (CP) is a chronic condition of abnormal motor function that begins shortly after birth and often worsens over time. CP adversely affects the child's development and impacts family and community. An intense series of physiotherapies administed early in life can harness the phenomenal capacity of the young brain to stimulate uninjured neurons to replace injured ones and improve function. An early and intense approach will change the current standard of care and lessen the 'burden' on families and the cost to society.

4.7 Resources

FACILITIES:
Mel & Enid Zuckerman College of Public Health
Arizona Health Sciences Center
University of Arizona Health, Tucson, AZ

Laboratory:
Not Applicable

Clinical:
The University of Arizona is a Research 1 University and in this regards has state-of-the art teaching and research facilities available to the students and trainees. These resources are briefly described below.

Library/Information Resources
The University of Arizona offers three libraries (Main, Science-Engineering, and Arizona Health Sciences Library - AHSL) on campus. The Main library system, which contains the Science – Engineering Library) contains almost 7,000,000 items, displaying 4,000 plus periodicals, books, microforms, maps, government publications, manuscripts and non-book media. In addition, the AHSL meets the needs of the Colleges of Medicine, Nursing, Pharmacy, and Public Health, and the health-related Internship graduate programs as well as the University Medical Center. This AHSL contains over 212,000 volumes and receives approximately 2,100 periodical and serial publications. The collection includes books, journals, audiovisuals, electronic resources, and other materials in the health sciences. It has on-line journals. The AHSL provides wireless access for faculty and students in the COPH.
College of Public Health - Computer Facilities and Resources

"The Arizona College of Public Health acts with respect and integrity to continuously advance health and well-being for all through knowledge, collaboration, empowerment, advocacy and sustainability. Our core values are: Fairness, Trust, Equity, Social Justice, Excellence, Innovation, Commitment, Collegiality, Diversity, Open Communication, Participation, Consensus and Enhancement. We strive to foster an educational community that values innovation and excellence in teaching, creation and dissemination of knowledge, practice-based research and research-based practice to address the health needs and interests of individuals and communities."

Although the clinical therapies will be administered at the Phoenix Children's Hospital and the Tucson Medical Center, the COPH will provide administrative and clinical support to the Principal Investigator, the Biostatitican and to the Evaluators who will be scoring the research video tapes. The College of Public Health has its own building, Drachman Hall that was completed in 2005 and provides over 23,800 gross assignable square feet (GASF) of permanently assigned space. This new space houses the College's administrative and support offices, divisions, educational programs, research programs (such as the Rural Health Office, Border Health Initiatives, Prevention Research Center, etc.), and employee offices (faculty, research staff, and students). Some research programs will remain off-site due to their unique program needs and requirements for a community setting. The new instructional area includes: three lecture halls with 125 workstations each; one distributed learning classroom; two collaborative classrooms with 60 workstations each; two collaborative classrooms with 40 work stations each; one collaborative classroom with 20 workstations; and one computer classroom that will be able to accommodate 50 students. In addition, twelve breakout or discussion rooms

and related service areas will be available for instructional or research needs. Interactive teleconference rooms will be housed within Drachman Hall and these rooms are equipped to broadcast and video stream presentations.

The building includes ample office space; each faculty office is 110 square feet and has a built-in lockable cabinet, voice over internet telephone service and two network Ethernet connections. There are two wireless systems throughout the COPH building, one is public access and the other is password protected for students and employees. Students and trainees have a study cubicle that is hardwired to the COP network system. The information technology office has seven servers that include three domain controllers, one web server, two development servers, and two sequal data base servers. The COPH building has a one Gigabit pipe for high speed internet service.

The computing infrastructure for the COPH consists of 18 servers predominately running on Windows NT or Windows 2000. These servers are used for a variety of purposes including email, web hosting, file sharing, authentication, virtual private networking (VPN), network printing and other special applications, such as survey management and data analysis.

The College's faculty and staff use approximately 300 personal computers provided from either departmental, college or research-funded resources. These are all Windows (Win98, Win NT, and Win2000) based systems connected to the network in a variety of ways depending on location. On-campus locations enjoy the network speed of the campus backbone (10 or 100 Mb/sec), two sites use wireless connections to establish connectivity, and the remainder use DSL technology.

Student access to computing technology is facilitated through the AHSL and Learning Resource Center. These facilities provide students with access to special technologies, and local and Internet resources. In addition, the Center for Computing and Information Technology, on the UA main campus, provides similar access to computing labs and resources. A help desk is available at each of these facilities.

Animal:
Not Applicable

Computer:
The budget allows for the purchase of a lap computer, a shared laser printer and a shared ink jet printer available as workstations for study personnel, and all faculty and the database manager each have their own computer station with site licenses for relevant Microsoft Office, SPSS, and STATA software.

The Division of Biomedical Communications at the Arizona Health Sciences Center provides communications media planning and production services in support of the instructional, research, and public services programs of the College of Medicine. They will provide the video production and duplication services for data collection. They will also provide systems administration and operations services for hosting the web-based data collection system.

Office:
All investigators and staff will have office space in their respective departments that is sufficient to meet their level of effort for the project.

Phoenix Children's Hospital, Phoenix, AZ
Outpatient Rehabilitation Center, Thomas Campus
Located in East Building on the 1st floor
Frances H. McClelland Pediatric Rehabilitation Center
1919 E. Thomas Rd
Phoenix, AZ 85016

Clinical – potential child enrollment:
During the past two years (2011 and 2012), 270 children less than 3 years of age with a diagnosis of cerebral palsy were seen at the Phoenix Children's Hospital (PCH). Each day, therapies (physical, occupational, or speech) are administered to 80 children in the current outpatient facilities on the Thomas Campus of the PCH. Another 40 children are seen in PCH satellite facilities.

The Outpatient Rehabilitation Center area has dedicated Registration, Rehabilitation waiting areas, 3 open GYMS and 7 treatment rooms, 2 large hallways, and therapists' work stations. In addition, there is a therapeutic playground outside the building, adjacent to Frances McClelland Pediatric Rehabilitation Center. Rehabilitation equipment is suitable to treat children 0-21 years of age.

Space:
Gyms
R#1176 GYM 341 sq. ft. (21.3x16)
R#1170 GYM 473 sq. ft. (25.3x18.7)
R#1152 GYM 1250 sq. ft. (26.7x46.7)

Seven (7) Treatment rooms, each measures 16 x 12 feet or 192 sq. ft.
R#1131 R#1133 R#1135 R#1137 R#1139 R#1141 R#1143

Rehabilitation waiting area: 1476 sq. ft. (69.3x21.3)
Rehabilitation Corridor I for ambulation/mobility training: 521 sq. ft. (9.3x56)
Rehabilitation Corridor II for ambulation/mobility training: 1179 sq. ft. (8.8x138.7)

One of the smaller gyms (R#1176 or R#1170) will be dedicated for the camera equipment for recording of subject evaluation sessions.

Department of Radiology - Clinical MRI Department:
All clinical imaging at PCH, directed by Dr. Miller, takes place within the Main Tower within the Department of Radiology at PCH. This department currently contains two clinical MRI systems with a third scheduled for installation in Summer 2013. After this installation, the facility will house two state-of-the-art Philips Ingenia 3T Multitransmit scanners that will be utilized for all human neuroimaging in the Program Project. The scanner has force-balanced, shielded gradients capable of 45 mT/m and 200 mT/m/ms, 70 cm ID cylindrical-bore magnet. Two recently released all-digital receiver 32-channel head coil are available for use. The scanner rooms are equipped with a physiological monitoring station allowing respiratory rate, end tidal CO2, SPO2, and heart rate to be monitored during examinations. The MRI facility is maintained by Philips service engineers and currently meets or exceeds all manufacturer specifications for performance. Functional neuroimaging capability is supported by an audio and visual stimulus presentation system (Esys) with MRI compatible headphones and reflective goggles (Invivo, Gainsville, FL). PCH has signed a master research agreement with Philips Healthcare that provides access to the latest MR sequence software including pseudocontinuous Arterial Spin

Labeling (pcASL) and Susceptibility Weighted Imaging with the padre filter (pSWI). The lead full-time MRI technologist, Ms. Amber Pokorney, is resident at the MRI facility and assists with all aspects of MRI exams including subject care, MRI scanning as well as data and image transfer. Ms. Pokorney is a former Philips MR Applications Specialist with extensive expertise and skill to ensure the quality and success of the studies. Dr. Jeffrey Miller is the Director of MRI. He is a board-certified (ABR) Radiologist with a Certificate of Added Qualification (CAQ) in Neuroradiology. He is a consultant for Philips Healthcare on advanced MR capabilities and the Ingenia 3T. The Neuroradiology section of the PCH Department of Radiology is staffed by 4 dedicated full-time ABR and CAQ neuroradiologists.

Tucson Medical Center, Outpatient Pediatric Therapies, Tucson, AZ

Clinical – potential child enrollment:

The director of the rehabilitation center estimates that each year at least 25 new children between the ages of 12 and 36 months are enrolled in therapy. The clinic was able to enroll 20 children between the ages of 18 and 36 months with cerebral palsy over a two year period in a feasibility study we have just completed. We do not anticipate any problems enrolling 30 children in the proposed study over the 3½ years when patients will be recruited.

This facility sees more than 275 pediatric therapy visits each week, with capacity determined by staffing. Space is shared with pediatric Speech/language Pathology with pediatric Audiology nearby. Staff for each discipline is trained in therapeutic techniques which include Perception-Action methodologies, and therapist education in this area is encouraged. The number of patients to be enrolled in this proposal and treated in this facility was thoughtfully considered as appropriate given the size of the clinic and the staffing of the clinic. The needs of the children identified in this project match those of the children we already treat, though the intensity of treatment would be the variant. This number of children and the number of visits required will be incorporated into the flow of the clinic patients.

Space:

Tucson Medical Center Pediatric Therapies is a clinic with 2 gym areas and several therapy rooms that are used for evaluations and some treatments. The pediatric gyms allow for more than one patient to be treated in the area with the patient's therapist and family present. Every session encourages family participation. The smaller gym is more enclosed, and can be used for 2 children/families, whereas, the second gym allows for 4 children at one time. There are 4 dedicated small rooms for Occupational and Physical therapies, though there are other spaces that can be used by these disciplines as needed. The small therapy rooms allow for the privacy needed during evaluation, conversations, and children who have immunosuppressed systems or who are easily distracted or and are not able to participate in a more open space. A covered playground is considered another treatment area, since the playground equipment was chosen by PT/OT for specific developmental tasks, including stair climbing, balance, and even independent sitting. In Arizona, the playground can be used almost every day, except midday on the hottest days of the summer.

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | * First Name: Burris | Middle Name: R.
* Last Name: Duncan | Suffix: M.D.
Position/Title: Professor Emeritus | Department: Public Health
Organization Name: Arizona Board of Regents, University of Arizona | Division: Health Promotion Sciences
* Street1: 1295 N. Martin Avenue, Building 202A
Street2:
* City: Tucson | County/ Parish: Pima
* State: AZ: Arizona | Province:
* Country: USA: UNITED STATES | * Zip / Postal Code: 85724-5163
* Phone Number: 520-907-7865 | Fax Number: 520-626-6093
* E-Mail: bduncan@peds.arizona.edu

Credential, e.g., agency login: DUNCANB

*** Project Role:** PD/PI | **Other Project Role Category:**

Degree Type: MD
Degree Year: 1958

***Attach Biographical Sketch** 1254-BiosketchDuncan.pdf [Add Attachment] [Delete Attachment] [View Attachment]
Attach Current & Pending Support [Add Attachment] [Delete Attachment] [View Attachment]

PROFILE - Senior/Key Person 1

Prefix: | * First Name: Chengcheng | Middle Name:
* Last Name: Hu | Suffix: Ph.D
Position/Title: Associate Professor | Department: Public Health
Organization Name: Arizona Board of Regents, University of Arizona | Division: Epidemiology and Biostatics
* Street1: 1295 N. Martin Avenue, Building 202A
Street2:
* City: Tucson | County/ Parish: Pima
* State: AZ: Arizona | Province:
* Country: USA: UNITED STATES | * Zip / Postal Code: 85724-5163
* Phone Number: 520-626-7914 | Fax Number: 520-626-2767
* E-Mail: hucc@email.arizona.edu

Credential, e.g., agency login: CHENGHU

*** Project Role:** Other (Specify) | **Other Project Role Category:** Biostatistician

Degree Type: Ph.D.
Degree Year: 2001

***Attach Biographical Sketch** 1255-BiosketchHu.pdf [Add Attachment] [Delete Attachment] [View Attachment]
Attach Current & Pending Support [Add Attachment] [Delete Attachment] [View Attachment]

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 2

Prefix: | * First Name: Theodore | Middle Name: P.

* Last Name: Trouard | Suffix: Ph.D

Position/Title: Associate Professor | Department: BIO5 Biomedical Enginneering

Organization Name: Arizona Board of Regents | Division:

* Street1: 1657 E. Helen Street

Street2: TW Keaning Bioresearch Bldg Room #131A

* City: Tucson | County/ Parish: Pima

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 85719-4511

* Phone Number: 520-626-2177 | Fax Number: 520-621-6555

* E-Mail: trouard@email.arizona.edu

Credential, e.g., agency login: TROUARD

*** Project Role:** Co-Investigator | **Other Project Role Category:**

Degree Type: Ph.D.

Degree Year: 1991

***Attach Biographical Sketch**	1256-BiosketchTrouard.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment	View Attachment

PROFILE - Senior/Key Person 3

Prefix: | * First Name: Jorge | Middle Name:

* Last Name: Arango | Suffix: M.D.

Position/Title: Research Scientist | Department: Barrow Neurological Institute

Organization Name: Phonenix Children's Hospital | Division:

* Street1: 1919 East Thomas Road

Street2:

* City: Phoenix | County/ Parish:

* State: AZ: Arizona | Province:

* Country: USA: UNITED STATES | * Zip / Postal Code: 85016-7710

* Phone Number: 602-933-0964 | Fax Number: 602-933-0059

* E-Mail: jarango@phoenixchildrens.com

Credential, e.g., agency login: JARANGO

*** Project Role:** PD/PI | **Other Project Role Category:**

Degree Type: M.D.

Degree Year: 2001

***Attach Biographical Sketch**	1257-BiosketchArango.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment	View Attachment

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 4

Prefix:		* First Name: Ewa	Middle Name:
* Last Name: Brandys		Suffix: M.D.	
Position/Title: Division Chief, Pediatrics		Department: Rehabilitation Services	
Organization Name: Phoenix Children's Hospital		Division: Barrow Neurological Institute	
* Street1: 1919 East Thomas Road			
Street2:			
* City: Phoenix		County/ Parish:	
* State: AZ: Arizona		Province:	
* Country: USA: UNITED STATES		* Zip / Postal Code: 85016-7710	
* Phone Number: 602-933-0435		Fax Number: 602-933-0445	
* E-Mail: ebrandys@phoenixchildrens.com			

Credential, e.g., agency login: EBRANDYS

*** Project Role:** Co-Investigator **Other Project Role Category:**

Degree Type: MD

Degree Year: 1986

***Attach Biographical Sketch**	1258-BiosketchBrandys.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment	View Attachment

Tracking Number:GRANT11413275 Funding Opportunity Number:PA-11-260 Received Date:2013-06-04T14:21:06-04:00

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Burris R. Duncan	Professor Emeritus Formerly Professor of Pediatrics & Public Health
eRA COMMONS USER NAME DUNCANB	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Washington University, St. Louis, Missouri	B.A.	1954	Liberal Arts
University of Kansas, Kansas City, Kansas	M.D.	1958	Medicine
DC General Hospital, Washington, DC		1958-1959	Rotating Internship
University of Maryland, Baltimore, MD		1959-1960	Pathology
St. Christopher's Hospital for Children, Philadelphia, PA		1962-1965	Pediatrics

A. Personal Statement

I have participated in clinical research for more than 50 years and have published over 60 articles in peer-reviewed journals and recently wrote a chapter on Cerebral Palsy in Genetics of Developmental Disabilities edited by MG Berlin and J Meaney.

Although I am past retirement age, I have no intention of retiring. I did stop seeing patients about 4 years ago and was given Professor Emeritus status. I am now teaching four graduate level courses at the College of Public Health and advice more than a dozen candidates for the Master of Public Health degree. I do not collect a full-time salary but am at the College at least 40 hours each week and continue with academic work at home for another 20 hours each week. I am very healthy and have no plans on slowing down.

On completing my pediatric residency in 1965 I started my career as Associate Director of the Birth Defects Center at the University of Colorado. Since then I have been caring for children with special needs and over the ensuing years developed a special interest in children with cerebral palsy. I was disappointed in the lack of improvement of some of these children despite the enormous time commitment of very involved ad dedicated parents and the efforts of physical and occupational therapists. I thought there must be a better way. Over a decade ago when on a trip to mainland China, I was exposed to another way. I learned that care providers there as well as in some other countries have different approaches. One such approach was acupuncture and cranial sacral osteopathic manipulation. Another was hippotheray. However, the most intriguing and what has proven to be the most effective is early and intense physiotherapies and this intervention has theoretical justification in neural plasticity.

I have been the PI on several investigations to evaluate other ways of managing children with CP. The first involved cranial sacral manipulation and acupuncture and was part of a $5 million NIH grant to establish a Center for Complementary and Alternative Medical Research in the Department of Pediatrics at the U. of Arizona. The next study evaluated hippotherapy as a means to decrease muscle tone in children with spastic CP. Then we conducted a joint project between the Beijing Children's Hospital and the Department of Pediatrics at the University of Arizona that was funded by the Arizona Disease Control Research Commission. That study was designed to compare the standard of care (SOC) in China (a package of 4 different therapies administered 5 times each week for 12 weeks) with therapies that are the SOC in the U.S. but administered only once each week. Coordinating this bi-national project meant trips to China every 3 to 4 months and it meant dealing with a very different culture and avoiding any major slips. I was able to successfully coordinate that bi-national project. The results supported an intervention of intense physiotherapies begun at an early age. However, we clearly understood that applying such an intense approach that is the SOC in China to young children might be difficult in the States. So, we embarked on a feasibility study in Tucson involving children between the ages of 18 and 36 months to address the question: Would parents take their child to the therapist office 5 times a week for 12 weeks? Despite the inconvenience, parents in this study did comply at a rate of 81% and their children did improve. The therapists were eager to be assigned these children as they saw the

improvement in function. The changes were confirmed by standard objective tests. Neuroplasticity is the theoretical basis of why this approach works. The capacity of the young brain to be reprogramed is there waiting to be harnessed. It is now time to perform a larger study based on our previous work. If we can confirm the findings of our earlier studies, there will be growing evidence to gradually change the current standard of care in the U.S. for children with cerebral palsy.

B. Positions and Honors

1965-1967 Associate Director, Birth Defects Center, University of Colorado Med Center
1967-1972 Assistant Professor, Dept. of Pediatrics, University of Colorado Med Center
1972-1975 Associate Professor, Dept. of Pediatrics, University of Colorado Med Center
1970-1975 Director, Pediatric Outpatient Dept., University of Colorado Med Center
1975-1978 Visiting Professor, Dept. of Pediatrics, Federal U. of Rio Grande do Norte, Natal, Brasil
1975-1978 Director of Project HOPE's Land Based Program, Natal, Brasil
1978-1984 Associate Professor of Pediatrics, U. of Arizona Health Sciences Center (AHSC)
1981-1986 Section Chief, General Pediatric Section, Dept. of Pediatrics, AHSC
1984-2005 Professor of Pediatrics, Dept. of Pediatrics, AHSC
1997-2005 Professor of Public Health, AHSC
1997-2005 Primary Care Physician, Children's Clinic for Rehabilitative Services
2006-present Professor Emeritus, University of Arizona

Consultant for Project HOPE:

Fortaleza, Brasil. Primary Health Care Project, 3 months 1988
Malawi, Africa. Child Survival Project, 1 month – 1989 Maternal Mortality Community Survey
Dominican Republic. Feasibility and Appropriateness of a New Children Hospital, 10 days - 1990
Dominican Republic. Development of Child Survival Program in Peri-urban Slum Area Santo Domingo, 11/91

National and International Offices (selected as pertinent to this grant):

1988-1989 American Academy of Pediatrics (AAP) Chairman: Task Force for International Child Health
1989-1993 Chairman: Provisional Committee for International Child Health AAP
1993-1996 Chairman: Committee for International Child Health AAP
1996-2000 Chairperson: Section on International Child Health AAP
1993-1997 Chairman: Steering Committee of the AAP's Pediatric Division of Health Volunteers Overseas
1995-1998 US Coordinator for HVO's Program in Uganda
1999-2004 Standing Committee of the International Pediatric Association
2001-present Co-Editor Newsletter for the Section on International Child Health AAP

Honors and Awards:

Duncan, B.R., and Schmitt, B.D.: Teaching Award, Western Society for Pediatric Research, Ross Laboratories, Carmel, California, January, 1973.
Homenagem from the Residentes e Faculdade de Pediatria of the U Federal do Rio Grande do Norte (Natal, Brasil, July, 1978).
Diploma de Socio Honarario from the Sociedade de Pediatria do Rio Grande do Norte (Natal, Brasil, 7/78).
Medalha de Merito Universitario Grau de Grande Conselheiro from the U Federal do Rio Grande do Norte (Natal, Brasil, August, 1978).
Otitulo Honorifico de Cidadao Natalense from the Camara Municipal do Natal (Brasil, August, 1978)
Homenagem from the Departamento de Enfermagem (Nursing) of the U Federal do Rio Grande do Norte (Natal, Brasil, August, 1978).
Homenagem from the Secretario de Saude do Rio Grande do Norte (Natal, Brasil, August, 1978).
Certificate of Recognition by the Arizona Occupational Therapy Association. (Phoenix, Arizona, April, 1988)
One of 16 Clinical Faculty nominated by U of AZ Medical School Class of 1989, 1990 and 1994 for Clinical Teacher of the Year.
Dean's List for Excellence in Teaching in the Clinical Sciences. October, 1992.
Certificate of Appreciation to Medical Education of the Class of 1995 The U. of Arizona, College of Medicine
Certificate for Outstanding Service to Children. Presented as part of the recognition of St. Andrew's Crippled Children's Clinic: A Jubilee Ministry. Nogales, AZ. September, 1993.
Dean's List for Excellence in Teaching in the Clinical Sciences. April, 1995
Honored: "Advocating for Health Care Rights: Making a Difference. Arizona Center for Disability Law: 11/12/98

Rosa Award: Tucson Health Care Provider of the Year for Disabled Persons. 2003
Academy of Pediatrics AZ Chapter's Achievement Award 2003-Exceptional work to increase Access to Health.
Appreciation and Recognition "Extraordinary Doctor and Citizen" presented by the Mayor of Tucson, 9/05
A Garden dedicated to Burris Duncan by the Children's Rehabilitation Clinic, September, 2005
Distinguish Service Award presented by Association of Pakistani-Descent of NA AZ Chapter, October, 2005
A finalist for the 2007 Volunteer Center of SA Community of Hearts Award, August, 2007
Recognition of 'Altruistic Labor' by the Community of Nogales, Sonora, Mexico, October, 2008
Assoc. of U. Centers on Disabilities (AUCD) 2011 Multicultural Council Award for Leadership in Diversity presented to the Sonoran UCEDD's Border Communities Workgroup Border Conference on Disabilities
The 2011 Vernon and Virginia Furrow Award for Excellence in Clinical Science Teaching for Medical Students
Andy Nichols Award from Arizona Mexican Commission: Wheelchair construction workshop 6/2012

C. Selected Peer-reviewed Publications

Kirsch WM, **Duncan BR**, Black FO, Stears JC. Laryngeal palsy in association with myelomeningocele, hydrocephalus, and the arnold-chiari malformation. J Neurosurg. 1968 Mar;28(3):207-14.
Frankenburg WK, **Duncan BR**, et al: Maternal Phenylketonuria: Implication on Growth and Development. J Pediatr 1968:73;560 570.
Rachesky I, Boyce WT, **Duncan B**, Bjelland J, Sibley B: Clinical Prediction of Cervical Spine Injuries in Children. AJDC. 1987:141;199 201.
Duncan B, Barton LL, Lloyd J, Marks-Katz M. Dietary considerations in osteopenia in tube-fed nonambulatory children with cerebral palsy. Clin Pediatr (Phila). 1999 Mar;38(3):133-7.
Shrestha AK, **Duncan B**, Taren D, Canfield LM, Greivenkamp JE, Shrestha N, Shrestha KK. A new, simple, inexpensive means of testing functional vitamin A status: the night vision threshold test (NVTT). A preliminary field-test report. Journal of Tropical Pediatrics. 2000;46(6):352-6.
Mauersberger K, Artz UK, **Duncan B**, Gurgevich S. Can children with cerebral palsy use self-hypnosis to reduce their muscle spasticity. Integrative Medicine 1999;2:93-96.
Ferreira J, **Duncan B**. Biofeedback-assisted hypnotherapy of warts in an adult with developmental disabilities: a case report. Alternative Therapies in Health and Medicine. 2002; 18(3):140-2.
Sanders H, Davis MF, **Duncan B**, Meaney FJ, Haynes J, Barton LL. Use of Complementary and Alternative Therapies Among Special Needs Children. Pediatrics 2003;111(3):584-7.
Duncan B, Barton L, Edmonds D, Blashill BM. Parental perceptions of the therapeutic effect of osteopathic manipulation or acupuncture in children with cerebral palsy. J Clinical Pediat 2004;43:349-553.
Davis MF, Meaney FJ, **Duncan B**. Factors influencing the use of complementary and alternative medicine in children. J Alternative & Complementary Medicine. 2004;10(5):740-2.
Elliott SP, Villar R, **Duncan B**. Evaluation and management of bacteriuria in patients with spina bifida and neurogenic bladder: a multicenter survey. J Urology 2005;173(1):217-20
Davis MF, Worden K, Clawson D, Meaney FJ, **Duncan, B**. Confirmatory Factor Analysis in Osteopathic Medicine: Fascial and Spinal Motion Restrictions as Correlates of Muscle Spasticity in Children With Cerebral Palsy. J Am Osteopath Assoc 2007 107:226-232.
Duncan B, McDonough-Means S, Andrews J, Worden K, Schnyer R, Meaney FJ. The effectiveness of cranial sacral osteopathic manipulation or acupuncture as complementary treatments for children with spastic cerebral palsy. J Am Osteopath Assoc 2008;108 559-570.
Duncan B, Harris G, Reedy J, Krahe S, Gillis R, Laguna L. Common/Unity: an innovative program to address three root causes of many of the social ills seen in adolescents. Clinical Pediatrics 2008;47(3):280-288.
McGibbon NH, Benda W, **Duncan B**, Silkwood-Sherer D. Immediate and long-term effects of hippotheray on symmetry of adductor muscles activity and functional ability in children with spastic cerebral palsy. Arch Phys Med Rehabil 2009;90(6):966-74.
Han T-L, Gray N, Vasquez M, Zou L-P, Shen K, **Duncan B**. Comparison of the GMFM-66 and the PEDI Functional Skills Mobility Domain in a Group of Chinese Children with Cerebral Palsy. Child Care Health Dev. 2011;37(3):398-403. doi: 10.1111/j.1365-2214.2010.01149.x. Epub 2010 Sep 5.
Duncan B, Mandalakas A, Staton D, Anders B, Kurbasic M, Nakakeeto M, Mustafa G, Reyes A, Evangelista D. Child Healthcare Workers in Resource-Limited Areas Improve Health With Innovative Low- Cost Projects. J Trop Pediatr 2012 58: 120-124.

Duncan B, Zou L-P, Han T-L, Shen K, Zhegh-L L, Zheng H, Walsh M, Venker C, Su Y, Schnyer R, Caspi O. Evaluating intensive rehabilitation therapies with and without acupuncture for children with cerebral palsy: a randomized controlled trial. Arch Phys Med Rehabil 2012;93:808-815.

Chapter in medical textbook relevant to grant proposal: Cerebral Palsy Duncan, B. Chapter in Genetics, Developmental Disabilities Eds. Butler MG, Meaney FJ.Marcel Dekker. 2005.

D. Research Support

Duncan, B (PI) U. of Arizona Foundation Wheel chair construction project In Nogales, Sonora, Mexico	$10,000
Duncan, B (PI) Rotary International Sonoran Durable Medical Equipment Construction Project in Nogales, Sonora, Mexico	$39,500
Basford T. University Center of Excellence in Developmental Disabilities 5 years	$500,000/year
Taren D.(PI) Decreasing MCH Health Disparities Through Graduate Education.	$1,879,000.
Duncan, B (PI) Arizona Disease Control Research Commission Acupuncture as Complementary Therapy for Cerebral Palsy	$523,982

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Hu, Chengcheng	Associate Professor of Public Health
eRA COMMONS USER NAME (credential, e.g., agency login) CHENGHU	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Peking University, Beijing, China		90-93	Mathematics
Johns Hopkins University, Baltimore, MD	M.A.	05/95	Mathematics
University of Washington, Seattle, WA	M.S.	08/98	Biostatistics
University of Washington, Seattle, WA	Ph.D.	08/01	Biostatistics
Harvard School of Public Health, Boston, MA	Postdoctoral	06/02	Biostatistics

A. Personal Statement

I have the expertise and experience to provide statistical support for this grant. For nearly seven years I served as a Senior Statistician for the NIH funded multicenter and multidisciplinary Pediatric AIDS Clinical Trials Group (PACTG) and International Maternal-Pediatric-Adolescent AIDS Clinical Trials (IMPAACT) Group. In this position I provided statistical expertise and leadership in the design, conduct and analysis of HIV clinical trials of various types and phases, including Phase I/II, Phase III, and pharmacokinetic studies. After joining the University of Arizona I have served as Director of the Biometry Core on the Chemoprevention of Skin Cancer Program Project since 2008, and also served as Co-Director of the Pattern Analysis and Computational Biology Core on the Targets to Therapeutics in Pancreatic Cancer Program Project from 2009 to 2010. Currently I'm serving as the statistician for a randomized clinical trial testing statin in Phoenix firefighters. In addition to extensive experience in collaborative research, I have conducted methodological research in the areas of survival analysis, longitudinal data, and high-dimensional data.

B. Positions and Honors

Positions and Employment

1996-2001 Research Assistant, Fred Hutchinson Cancer Research Center, Seattle, WA
2001-2002 Research Fellow, Dept of Biostatistics, Harvard School of Public Health, Boston, MA
2001-2008 Senior Statistician, Ctr Biostatistics in AIDS Research, Harvard Sch Public Health, Boston, MA
2002-2008 Assistant Professor, Dept of Biostatistics, Harvard School of Public Health, Boston, MA
2008-2012 Assistant Professor, Division of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ
2012-present Associate Professor, Division of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ

Other Experience

2006 Adolescent Research Agenda Committee, NIAID/DAIDS Pediatric AIDS Clinical Trials Group
2009-2010 NIH/NCI Small Grants for Cancer Epidemiology (R03) Review Panel
2012-present Observational Safety Review Board for the study “Typical Daily Emotion, Ischemia and Repolarization in Coronary Heart Disease”

Honors

1989 Finalist and Third-Prize Winner, Chinese Mathematics Olympiad
1998 Donovan J. Thompson Award for Academic Excellence in Biostatistics, Univ Washington, Seattle, WA
1999 Best Written Paper, International Biometric Society (WNAR), Student Paper Competition

C. Selected Peer-reviewed Publications (out of 40 total)

1. Ellis WJ, Etzioni RD, Vessella RL, Hu C, Goodman GE. (2001). Serial prostate specific antigen, free-to-total prostate specific antigen ratio and complexed prostate specific antigen for the diagnosis of prostate cancer. J Urology, 166(1), 93-98; discussion 98-99. PMID11435831.
2. Hu C and Lin DY. (2002). Cox regression with covariate measurement error. Scand J Stat, 29(4), 637-655.
3. Hu C and Lin DY. (2004). Semiparametric failure time regression with replicates of mismeasured covariates. J Am Stat Assoc, 99,105-118.
4. Huang X, Wolfe RA, Hu C. (2004). A test for informative censoring in clustered survival data. Stat Med, 23(13), 2089-2107. PMID15211605
5. Wang KH, Majewska A, Schummers J, Farley B, Hu C, Sur M, and Tonegawa S. (2006). In vivo two-photon imaging reveals a role of Arc in enhancing orientation specificity in visual cortex. Cell, 126, 389-402. PMID16873068
6. Chen YQ, Hu C and Wang Y. (2006). Attributable risk function in the proportional hazards model for censored time-to-event. Biostat, 7, 515-529. PMID16478758.
7. Hu C and De Gruttola V. (2007). Joint modeling of progression of HIV resistance mutations measured with uncertainty and time to virological failure. Biometrics, 63, 60-68. PMID17447930
8. McKinney RE, Rodman J, Hu C, Britto P, Hughes M, Smith ME, Serchuk LK, Kraimer J, Ortiz AA, Flynn P, Yogev R, Spector S, Draper L, Tran P, Scites M, Dickover R, Weinberg A, Cunningham C, Abrams E, Blum HR, Chittick GE, Reynolds L, Rathore M, and Pediatric AIDS Clinical Trials Group Protocol P1021 Study Team. (2007). Long term safety and efficacy of a once-daily regimen of emtricitabine, didanosine, and efavirenz in HIV-infected, therapy-naive children and adolescents (Pediatric AIDS Clinical Trials Group protocol P1021). Pediatrics, 120(2), e416-e423. PMID17646352.
9. Healy BC, De Gruttola VG, and Hu C. (2008). Accommodating uncertainty in tree set for function estimation. Stat Appl Genet Mol Biol, 7(1) Article 5. Epub Feb 19. PMID18312210.
10. Stratton SP, Alberts DS, Einspahr JG, Sagerman PM, Warneke J, Curiel-Lewandrowski C, Myrdal PB, Karlage KL, Nickoloff BJ, Brooks C, Saboda K, Yozwiak M, Krutzsch MR, Hu C, Lluria-Prevatt M, Dong Z, Bowden GT, Bartels PH. (2010). A Phase 2a study of topical perillyl alcohol cream for chemoprevention of skin cancer. Cancer Prevention Research, 3(2), 160-169. PMID20103724.
11. Best BM, Stek AM, Mirochnick M, Hu C, Li H, Burchett SK, Rossi SS, Smith E, Read JS, Capparelli EV for the International Maternal Pediatric Adolescent AIDS Clinical Trials Group 1026s Study Team. (2010). Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. Journal of Acquired Immune Deficiency Syndromes, 54(4), 381-388. PMID20632458.
12. Hibler EA, Jurutka PW, Egan JB, Hu C, LeRoy EC, Martínez ME, Thompson PA, Jacobs ET (2010). Association between polymorphic variation in VDR and RXRA and circulating levels of vitamin D metabolites. Journal of Steroid Biochemistry and Molecular Biology, 121, 438-441. PMID20307661.
13. LeRoy EC, Moore J, Hu C, Martínez ME, Jacobs ET, Lance P, Duggan D, and Thompson PA. (2011). Genes in the insulin and insulin-like growth factor (IGF) pathway and odds of metachronous colorectal adenoma. Human Genetics, 129(5), 503-512. PMID21221997.
14. Hu C and De Gruttola V. (2011). Recursive partitioning of resistant mutations for longitudinal markers based on a U-type score. Biostatistics, 12(4), 750-762. PMID21596729.
15. Hibler EA, Hu C, Jurutka PW, Martinez ME, Jacobs ET. (2012). Polymorphic variation in the GC and CASR genes and associations with vitamin D metabolite concentration and metachronous colorectal neoplasia. Cancer Epidemiology, Biomarkers & Prevention, 21(2), 368-375. PMID22144504.

D. Research Support
Ongoing Research Support

NIH/NCI 5 P01 CA027502 (Alberts, PI) 10/01/08-6/30/16
Chemoprevention of Skin Cancer Program Project
The Biometry Core of this project is to provide data management and computing support for all projects and other cores, and collaborates with other investigators in the design, conduct and analysis of all studies.
Role: Director, Biometry Core

NIH/NCI 2 P30 CA023074 (Alberts, PI) 07/01/09-06/30/14
Arizona Cancer Center Core Support Grant
The Biometry Shared Service supports research at the Arizona Cancer Center, across the spectrum of clinical trials and prevention research, as well as basic and translational studies. The Shared Service is active in all phases of study design, operation, data management, statistical analysis, and manuscript preparation.
Role: Co-Investigator

5R01OH009469 (Burgess, PI) 09/01/09-08/31/13
CDC/NIOSH
Implementing Risk Management Strategies to Prevent Injuries among Firefighters
The goal of this project is to use a risk management approach to improve and implement selected standard operating guidelines and to determine their effectiveness in reducing fire department workplace injuries.
Role: Co-Investigator

EMW-2009-FP-00343 (Burgess, PI) 04/01/10-03/31/13
FEMA
Firefighter Statin Trial: Reducing Atherosclerotic Disease and Risk Factors
The goal of this project is to determine if statin therapy can prevent or reverse increases in early atherosclerotic disease in firefighters measured by carotid artery initma-media thickness.
Role: Co-Investigator

R01 OH009878 (Burgess, PI) 07/01/12 – 06/30/15
CDC/NIOSH
Comparison of Diesel and Biodiesel Emissions and Health Effects in Underground Mining
The goal of this grant is to evaluate and compare exposure to diesel and biodiesel emissions and acute health effects in underground mining.
Role: Co-Investigator

1U01CA153086 (Futscher, PI) 09/17/10-08/31/15
NIH/NCI
Epigenetic Features of Pregnancy-Associated Breast Cancer in Hispanic Women
The immediate objective of this research project is to compare the epidemiological and epigenetic profiles of breast cancer tumors diagnosed in the transient postpartum period of increased risk against those that are diagnosed outside this period.
Role: Co-Investigator

1R21AR060811 (Chen, PI) 09/01/11-08/31/13
NIH/NIAMS
A New Hip Fracture Risk Prediction Tool Based on Common Predictors and Hip Geometry
The overall goal of this study is to develop a comprehensive and flexible model to assess the risk of hip fracture for a specific woman. This will be achieved by constructing a novel predictor that classifies data that include hip structural geometry, sarcopenia measurements as well as risk factors identified in previous studies.
Role: Co-Investigator

Pending Research Support

EMW-2011-FP-00345 (Burgess, PI) 07/01/12 – 06/30/15
FEMA Assistance to Firefighters Grant Program
Comprehensive Health Economic Evaluation for the Fire Service
The goal of this project is to carry out an economic evaluation of fire department safety and health programs including determination of return on investment and improved allocation among health and safety program components.
Role: Co-Investigator

Completed Research Support

NIH/NCI 5 U01 CA128454 Cunningham (PI, sub-contract) 07/1/09-06/30/12
Tumor Glycomics Laboratory for Pancreatic Carcinoma
Role: Co-Investigator
The goal of this project is to apply newly developed glycomic technologies to the development of serum markers for pancreatic carcinoma.

HHSN261201100111C (McDonough, PI) 09/30/11-06/29/12
NIH/NCI
An Automated Karyometric Assay to Predict Response to Drugs That Reduce the Risk of Breast Cancer
This SBIR contract project is a collaboration between Vala Sciences Inc and the Arizona Cancer Center to develop an automated karyometric assay to predict response in studies testing the potential of drugs to prevent or reverse the development of precancerous lesions in women that are at high risk for breast cancer.

NIH/NIAID 5 R01 AI051164 De Gruttola (PI) Hu (subcontract PI) 06/01/09-11/30/11
Harvard School of Public Health
Methods for Long-Term Follow-Up of HIV-Infected Patients
The goal of this subcontract is to develop innovative statistical methods for the analysis of high-dimensional biomarkers.
Role: Subcontract PI

NIH/NCI 5 P01 CA109552 Von Hoff (PI) 07/01/09 -11/30/10
Targets to Therapeutics in Pancreatic Cancer
This Program Project contains three translational research projects whose collective aims are to develop new therapeutics for patients with pancreatic cancer.
Role: Co-Director of Pattern Analysis and Computational Biology Core

CDC/NIOSH 200-2008-24858 Burgess (PI) 01/01/09-11/01/09
Development of a Severe Injury Surveillance System for Hazard Identification and Guiding Technological Interventions
Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Theodore P. Trouard	Associate Professor of Biomedical Engineering Associate Professor of Medical Imaging
eRA COMMONS USER NAME (credential, e.g., agency login) TROUARD	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
California Polytechnic University, San Luis	B.S.	1981-1985	Physics
University of Virginia, Charlottesville, VA	Ph.D.	1986-1991	Biophysics
University of Umeå, Umeå, Sweden		1992-1993	Postdoc
University of Arizona, Tucson, AZ		1994-1995	Postdoc

A. Personal Statement

For the past 20 years, my interests and scientific efforts have been in the development and application of novel MRI methodologies to biomedical problems. Over the past several years, I have focused my research on development of novel techniques for imaging the brain. Improving diffusion-weighted MRI data acquisition, in particular, has been a major emphasis of my laboratory. In 1999, my lab developed a radial-MRI method for high-resolution DWMRI that is insensitive to bulk motion and the presence of magnetic field inhomogeneities. This technique has been applied to human imaging of stroke and cancer as well as preclinical imaging of mouse models of Niemann-Pick type C and Alzheimer's Disease. I have also been working for a number of years in the application of anatomical MRI, functional MRI and DTI to study cognitive processes and disease altering mechanisms in the human brain. The inherently interdisciplinary nature of my research and interests has given me the opportunity to collaborate with radiologists, pediatricians, neuroscientists, oncologists, geneticists, and engineers at the University's Colleges of Engineering, Medicine, and Sciences. My laboratory is set up well to perform the imaging and activities described in the exploratory aim.

B. Positions and Honors

Positions and Employment

6/84-9/85 Research Assistant, Central Research Department, Varian Associates, Palo Alto, CA.
9/85-12/87 Research Assistant, Department of Chemistry, University of Virginia, Charlottesville, VA.
1/88-12/91 Research Assistant, Department of Chemistry, University of Arizona, Tucson, AZ.
1/92-12/93 Postdoctoral Research Fellow, Department of Physical Chemistry, University of Umeå, Sweden.
1/94-5/95 Postdoctoral Research Associate, Department of Radiology, University of Arizona, Tucson, AZ.
6/95-8/00 Research Assistant Professor, Department of Radiology, University of Arizona, Tucson, AZ.
9/00-9/05 Assistant Professor, Department of Radiology, University of Arizona, Tucson, AZ.
9/00-9/05 Assistant Professor, Biomedical Engineering Program, University of Arizona, Tucson, AZ.
9/05-present Associate Professor, Department of Radiology, University of Arizona, Tucson, AZ.
9/05-present Associate Professor, Biomedical Engineering Program, University of Arizona, Tucson, AZ.
9/05-present Associate Professor, BIO5 Institute, University of Arizona, Tucson, AZ.
9/10-present Associate Professor, McKnight Brain Institute, University of Arizona, Tucson, AZ.
9/12-present Assistant Director, BIO5 Institute, University of Arizona, Tucson, AZ

Professional Affiliations and Other Experience

1993-present International Society for Magnetic Resonance in Medicine
2004-2009 NIH Peer Review Committee, Brain Disorders & Clinical Neuroscience, ad hoc reviewer
2003, 2007 NIBIB Peer Review Committee, ad hoc reviewer

Honors and Awards

2011 – present Arizona Engineering Education Fellow
1986 - 1988 Deans scholarship, University of Virginia
1995 - 1996 Flinn Post-doctoral Scientist, University of Arizona

C. Selected Peer-reviewed Publications (From >50 peer reviewed journal articles)

Most relevant to the current application

1. **Trouard TP**, Theilmann RJ, Altbach MI, and Gmitro AF (1999), High resolution diffusion imaging with DIFRAD-FSE (DIFfusion-weighted Radial Acquisition of Data with fast Spin-Echo), *Magn. Reson. Med.* **42**, 11-18.
2. Ryan L, Nadel L, Keil K, Putnam K, Schnyer D, **Trouard T**, and Moscovitch M. (2001), The hippocampal complex and retrieval of recent and very remote autobiographical memories: Evidence from functional magnetic resonance imaging in neurologically intact people, *Hippocampus* **11**, 707-714.
3. **Trouard TP**, Heidenreich R, Seeger J and Erickson RP (2005) Diffusion Tensor Imaging (DTI) in Niemann-Pick Type C Disease, Ped. Neurol., 5:325-330.
4. Lope-Piedrafita S, Garcia-Martin ML, Galons JP, Gillies RJ and **Trouard TP** (2008) Longitudinal Diffusion Tensor Imaging in a Rat Brain Glioma Model, NMR in Biomed. 21:799-808.
5. Walther K, Bendlin BB, Glisky EL, Trouard TP, Lisse JR Posever JO and Ryan L (2010) Anti-inflammatory drugs reduced age-related decreases in brain volume in cognitively normal older adults, Neurobiology of Aging 32:497-505.

Additional publications of importance to the field (in chronological order)

1. Schnyer DM, Ryan L, **Trouard TP**, and Forster K (2002), Masked word repetition results in increased fMRI signal: a framework for understanding signal changes in priming. *Neuroreport* **13**:281-284.
2. De Weerd P, Reinke K, Ryan L, McIsaac L, Perschler P, Schnyer D, **Trouard T**, & Gmitro A, (2003), Cortical mechanisms for acquisition and performance of bimanual motor sequences. *Neuroimage*, **19**:1404-1416.
3. Ryan L, Nadel L, Keil K, Putnam K, Schnyer D, **Trouard T**, and Moscovitch M. (2001), The hippocampal complex and retrieval of recent and very remote autobiographical memories: Evidence from functional magnetic resonance imaging in neurologically intact people, *Hippocampus* **11**, 707-714.
4. McCabe K, Houser D, Ryan L, Smith V, and **Trouard T** (2001), A Functional Imaging Study of "Theory of Mind" in Two-Person Reciprocal Exchange, *PNAS* **98**:11832.
5. Sarlls J, Gmitro AF, Altbach MI, and **Trouard TP** (2005) Isotropic Diffusion Weighting in Radial Fast Spin Echo (Radial-FSE) MRI. Magn. Reson. Med., 53:1347-1354.
6. Bendlin BB, **Trouard TP**, Ryan L (2007) Caffeine attenuates practice effects in word stem completion as measured by fMRI BOLD signal, Hum Brain Mapp.28:654-62.
7. Lope-Piedrafita S, Totenhagen J, Hicks C, Erickson RP and **Trouard TP** (2008) MRI Detects therapeutic Effects in Weanling Niemann-Pick Type C Mice. J. Neurosci. Res 68:2802-2807.

8. Totenhagen J, Lope-Piedrafita S, Thome K, Borbon I, Erickson RP and Trouard TP (2011) In Vivo Assessment of Myelination in Niemann-Pick Type C Mice across the lifespan via Quantitative T2 mapping and Diffusion Tensor Imaging. Journal of Magnetic Resonance Imaging 35:528-536.
9. Russell G, Harkins KD, Secomb TW, Galons JP and Trouard TP (2012) A Finite Difference Method for Large Scale Simulations of Water Diffusion in Tissue. Physics in Medicine and Biology 57: N35-N46.
10. Totenhagen J, Lope-Piedrafita S, Thome K, Borbon I, Erickson RP and Trouard TP (2012) 1H Magnetic Resonance Spectroscopy of Neurodegeneration in a Mouse Model of Niemann-Pick Type C1 Disease. Journal of Magnetic Resonance Imaging. In press.

D. Research Support

Ongoing Research Support

RO3 AG037806 (Trouard (PI) 06/01/11-05/31/13
NIH/NIA UTE MRI of Alzheimer's Mice
The goal of this project is to develop ultrashort TE MRI methodology to non-invasively measure amyloid beta deposition in mouse models of Alzheimer's disease
Role: PI (10%)

T32-EB000809 (PI: Gmitro) 08/01/08-07/31/13
NIH/NIBIB
Graduate Training in Biomedical Imaging and Spectroscopy
This is graduate training program in biomedical imaging and spectroscopy.
Role: Co-I (0%)

Completed Research Support

ABRC 8-078 Trouard (PI) 07/01/2008-06/30/2011
Arizona Biomedical Research Commission
MRI, MRS and Molecular Modeling of Three Dimensional Cell Cultures
The goal of this project is to use novel 3D hollow fiber bioreactor cell cultures as models for living tissue to understand changes seen in MRI and MRS following ischemic injury. Mathematical modeling of water diffusion in cells is also being developed to interpret results from these experiments.
Role: PI

RO1 EB00343-06 Trouard (PI) 02/01/2007-1/31/2012
NIH/NIBIB Non-Invasive Monitoring of NP-C Progression and Therapy with MRS/MRI
The goal of this project is to develop a non-invasive and quantitative method to monitor the progression of NPC disease and its response to successful therapy.
Role: PI

R01 CA119046 Stopeck (PI) 07/01/06-06/30/2011
NIH/NCI Diffusion MRI as Biomarker for Therapy Response in Breast Cancer Metastases
The goal of this project will be to test the hypotheses that early increases in the ADC presage clinical response in liver, bone and brain metastases.
Role: Co-I

R01 NS044107 Ryan (PI) 03/01/2003 – 02/29/2008
NIH-NINDS fMRI studies of Semantic and Episodic Memory Retrieval
This project used functional MRI to investigate the common and differential brain structures and pathways involved in semantic and episodic memory.
Role: Co-I

RO1 EB00343 Trouard (PI) 04/01/2001-9/30/2006
NIH/NIBIB Non-Invasive Monitoring of NP-C Progression and Therapy with MRS/MRI
The goal of this project is to develop a non-invasive and quantitative method to monitor the progression of NPC disease and its response to successful therapy.
Role: PI

R21 RR14274 Trouard (PI) 08/01/99–07/31/02
NIH/NCRR
High-resolution Diffusion-Weighted MRI of the Brain
The primary goal of this project is to develop a MRI method for high-resolution diffusion-weighted imaging of the human brain.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Jorge I. Arango, MD	Research Scientist Barrow Neurological Institute Phoenix Children's Hospital, Phoenix AZ
eRA COMMONS USER NAME (credential, e.g., agency login) JARANGO	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Universidad de Antioquia, U de A	MD	04/01	Medicine
University of Texas Health Science Center at San Antonio	Fellowship	11/05	Clinical Research
University of Texas Health Science Center at San Antonio	MS	06/06	Clinical Research
Arizona State University	MS	12/11	Research Management

A. Personal Statement:

My research focus is in neural injury, the mechanisms for its mitigation and the identification of effective mechanisms for neuronal recovery. My role as a co-investigator for the project evaluating the benefits of intensive therapy over standard therapy in patients diagnosed with cerebral palsy will include the implementation and oversight of all study activities performed at PCH along with the continuous evaluation of study findings. I truly believe the intervention proposed in this research will define a model in the management of patients with cerebral palsy and their functional recovery. My role in this project will pair with an initiative I am leading, intended for the automatic identification and data tracking of newly born patients in risk for the development of cerebral palsy.

B. Positions and Honors

Positions and Employment

2003 Staff Physician, Hospital San Juan de Dios La Ceja, La Ceja, Colombia
2005 – 2007 Senior Research Associate, University of Texas Health Science Center at San Antonio
2007 – 2008 Clinical Research Manager, Banner Alzheimer's Institute, Phoenix, AZ
2008 – 2011 Independent Clinical Research Consultant, Phoenix, AZ
2011 – pres. Research Scientist, Phoenix Children's Hospital, Phoenix, AZ

C. Peer-reviewed Publications

Freytes CO, Ratanatharathorn V, Taylor C, Abboud C, Chesser N, Restrepo A, **Arango JI**, Odenheimer D. Phase I/II randomized trial evaluating the safety and clinical effects of repifermin administered to reduce mucositis in patients undergoing autologous hematopoietic stem cell transplantation. Clinical Cancer Research. 2004 Dec; 10(24):8318-24.

Arango JI. Restrepo A. Schneider DL. Callander NS. Ochoa-Bayona JL. Restrepo MI. Bradshaw P. Patterson J. Freytes CO. Incidence of Clostridium difficile-Associated Diarrhea Before and After Autologous Peripheral Blood Stem Cell Transplantation for Lymphoma and Multiple Myeloma. Bone Marrow Transplantation, 2006 Mar; 37(5):517-21.

Cohn SM, **Arango JI**, Myers JG, Lopez PP, Jonas RB, Waite LL, Corneille MG, Stewart RM, Dent DL. Computed tomography grading systems poorly predict the need for intervention after spleen and liver injuries. The American Surgeon. 2009 Feb; 75(2):133-9.

Lopez PP, **Arango JI**, Gallup TM, Cohn SM, Myers JG, Corneille MG, Stewart RM, and Dent DL. Diaphragmatic Injuries: What has changed over a 20-Year Period? The American Surgeon. 2010 May; 76(5):512-6.

Sreeramoju P, Porbandarwalla NS, **Arango J**, Latham K, Dent DL, Stewart RM, Patterson JE. Recurrent skin and soft tissue infections due to methicillin-resistant Staphylococcus aureus requiring operative debridement. The American Surgeon. 2011 Feb; 201(2):216-20.

Arango JI, Deibert CP, Brown D, Bell M, Dvorchik I and Adelson PD. Posttraumatic seizures in children with severe traumatic brain injury. Child's Nervous System. 2012 July; 28(11):1925-29

D. Research Support

Ongoing Research Support

ADHS 13-1069 (Adelson, PI) 07/01/10 - 06/30/13
Arizona Biomedical Research Commission 04/15/11 - 06/30/13 (period on project)
A Practical Brain-Computer Interface Based on Micro-ECoG Technology
A translational effort to implement knowledge and experience gained from previous Brain-Computer Interface (BCI) research towards the micro-ECoG technology.
Role: Co-I

ADHS 13-031298 (Adelson, PI) 07/01/11– 6/30/14
Arizona Biomedical Research Commission
Rapid Cycle Outcomes Research to Improve Clinical and Operational Outcomes
A systematic solution to integrate multisource data for automatic tracking of quality control metrics and their utilization in outcome analysis.
Role: Co-I

Codman Neuro
Spatiotemporal dynamics and multimodal monitoring of pediatric patients in the Intensive Care Unit
Incorporation of multimodal neurophysiological monitoring for the identification of changes in brain dynamics and their use as outcome predictors and targets for care.
Role: Co-I; 8/15/2012-8/14/2014

United Cerebral Palsy (Arango, PI) 04/01/13 – 03/31/14
Neuro NICU Database. A Way to Improve Neurodevelopmental Outcomes
A web based system that allows NICU personnel to track patient management and to assess impact of care.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME:	POSITION TITLE
Ewa Brandys, MD	Division Chief, Pediatric Rehabilitation Medicine Medical Director of Rehabilitation Services
eRA COMMONS USER NAME (credential, e.g., agency login) EBRANDYS	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Jagiellonian University Medical College, Krakow	M.D.	02/86	Medicine
Srodmiescie Health Care Center, Krakow	Internship	6/86-6/87	Rotating Internship
St. Louis Hospital for Children, Krakow	Residency	7/87-4/91	Pediatrics
Polish-American Children's Hospital of the Jagiellonian University Medical College, Krakow	Fellowship	9/91-3/95	Physical Medicine and Rehabilitation
New York Flushing Hospital and Medical Center, Flushing, NY	Internship -	7/99-6/00	Transitional Year Program
Hospital of the University of Pennsylvania, Philadelphia, PA	Residency	7/00-6/03	Physical Medicine & Rehabilitation
Kennedy Krieger Institute, The Johns Hopkins University School of Medicine. Baltimore, MD	Postdoctoral Fellowship	7/03-6/05	Pediatric Rehabilitation Medicine, NIH T-32 Brain Injury Training Grant

A. Personal Statement

As a fellowship trained, board certified pediatric physiatrist, I work closely with the interdisciplinary team of specialists treating children with congenital and acquired disabilities including cerebral palsy (CP). My specialty training and extensive clinical experience in comprehensive rehabilitation of children with CP places me in excellent position to be a member of this research team. My role in the study will be as site Co-Investigator for the clinical site at Phoenix Children's Hospital. In that role I will perform the initial evaluation of each potential subject, confirm or diagnose CP, prescribe and supervise treatment, monitor each subject's course and rehabilitation needs during their enrollment. I will make sure that all children enrolled in the study receive the care necessary to optimize their level of functioning. I have the expertise, leadership and motivation necessary to successfully carry out the proposed work. I am aware of the importance of frequent communication among project members and of constructing a realistic research plan, timeline, and budget.

B. Positions and Honors

Positions and Employment

06/86-06/88 Physician. 'Srodmiescie' Health Care Center. Krakow, Poland.
07/88-09/89 Physician. 'Solidarnosc' Children's Rehabilitation Hospital. Radziszow, Poland.
10/89-05/95 Physician, Rehabilitation Medicine Consultant. Polish-American Children's Hospital of the Jagiellonian University Medical College. Krakow, Poland.
09/93-05/95 Physician Volunteer. Rehabilitation Medicine Consultant. Day Care Center for Physically and Mentally Challenged Adults. Krakow, Poland.
04/93-05/95 Physician Volunteer. Rehabilitation Medicine Consultant. Polish Association of Autism. Krakow, Poland.
02/94-05/95 Physician Volunteer. Rehabilitation Medicine Consultant. Group Home for Chronically Ill Children. Krakow, Poland.
05/96-07/97 Physical Therapy Technician. Danuta Janiszewski, M.D., Ph.D., P.C. New York, NY.
01/04-06/05 Physician, Associate Medical Staff. Kennedy Krieger Institute. Baltimore, MD.

07/05-08/07 Physician, Faculty and Active Medical Staff. International Center for Spinal Cord Injury Department and Pediatric Rehabilitation Department. Kennedy Krieger Institute, Johns Hopkins University School of Medicine, Baltimore, MD.
08/07-present Consulting Staff. Pediatric Rehabilitation Department. Kennedy Krieger Institute, Baltimore, MD.
08/07-present Consulting Staff. The Children's Institute. Pittsburgh, PA.
07/11-present Division Chief, Pediatric Rehabilitation Medicine. Phoenix Children's Hospital. Phoenix, AZ.

Other Experience and Professional Memberships

Academic Appointment

2005-2007 Clinical Instructor, Physical Medicine and Rehabilitation, Johns Hopkins School of Medicine. Baltimore, MD

Research Consultantships

01/93-10/93 Medical Consultant. PI: Czeslawa Frejlich, Ph.D., Adjunct Professor, The Faculty of Industrial Design of the Academy of Fine Arts. Krakow, Poland. Analyzed the ergonomic parameters of the standard Polish school desk and chair and explored their effects on posture development in students. Published in October 1993, in *Atest-Ochrona Pracy [The Magazine of the Organization of Occupational Hazards]*. Krakow, Poland.

08/05-06/07 Hunter's Dream for a Cure Foundation. Role: Physical Medicine and Rehabilitation specialist. Providing evaluation of patients seen in the Sturge-Weber Syndrome Clinical Center of Excellence at Kennedy Krieger Institute/Johns Hopkins Hospital.

Professional Societies

1999-present American Medical Association
1999-2000 Committee of Interns and Residents.
2002-2003 Pennsylvania Medical Society.
2001-present American Academy of Physical Medicine and Rehabilitation.
2006-2007 Maryland Society of Physical Medicine and Rehabilitation.
2006-2007 Association of Academic Physiatrists.
2009-present American College of Sports Medicine
2012-present American Academy of Cerebral Palsy and Developmental Medicine

Advisory Committees

1994-1995 Member of the Chartering Committee. The "Lajkonik" Association for Aid to Children with Disabilities at the Polish-American Children's Hospital. Poland.

2007-2011 Spinal Cord Injury Committee. Children's Institute, Pittsburgh, PA.

Consultantships

04/93-05/95 Polish Association of Autism. Volunteer. Rehabilitation Medicine Consultant. Krakow, Poland.

Licensure

Poland
06/86 Licensed to Practice Medicine. Poland.

USA
12/2002-active Pennsylvania Medical Physician and Surgeon License.
06/2003-active Maryland Medical Physician and Surgeon License.
06/2011-active Arizona Medical Board License.

Boards/Certifications

Poland

04/1991 Board Certification in Pediatrics.
03/1995 Board Certification in Physical Medicine and Rehabilitation.

USA

03/1998 USMLE Step 2.
06/1998 USMLE Step 1.
2/1998 ECFMG Clinical Skills Assessment.
01/1999 ECFMG Certificate.
05/2001 USMLE Step 3.
05/2003 American Board of Physical Medicine and Rehabilitation, Part I.
05/2004 American Board of Physical Medicine and Rehabilitation, Part II.
07/2004 Board Certification in Physical Medicine and Rehabilitation.
12/2006 American Board of Physical Medicine and Rehabilitation, subspecialty certification in Pediatric Rehabilitation Medicine.

Awards/Honors

2001-2002 AVENTIS/Lippincott Williams&Wilkins PMR Residents Scholarship.

2002 Research project: *The Prevalence of Abdominal, Groin and Perineal Symptoms in Patients with Internal Disc Disruption Syndrome* was selected for presentation during Musculoskeletal Grand Rounds at the 63rd American Academy of PMR Annual Assembly.

2012 Clinical rehabilitation program *I Can Walk Project* was awarded Leadership Circle Foundation Annual Grant $70,950. The project offers innovative gait training protocol for children with neurological deficits. Children with severe weakness/paralysis participate in intensive gait training using RTI600 robotic device which coordinates functional electric stimulation to leg muscles with motor support and patient own effort.

C. Selected Peer-reviewed Publications

1. Slipman CW, **Brandys E**, Isaac Z, Bhat AL, Gilchrist RV, Chou L. The Prevalence of Abdominal, Groin,and Perineal Symptoms in Patients With Internal Disk Disruption Syndrome. Poster-presented during 63rd Annual Assembly of the American Academy of PMR. Abstract published in *Archives of Physical Medicine and Rehabilitation.* 2002, vol. 83: 1664.

2. Lewelt A, **Brandys E**, Salorio C, Pidcock F. Spasticity and Daily Spontaneous Upper Extremity Use in Children with Hemiplegic Cerebral Palsy. Poster-presented during 68th Annual Assembly of the American Academy of PMR, 2007.

3. Lewelt A, **Brandys E**, Pidcock F. Quantification of Spontaneous Upper extremity Activity in Children with Hemiplegic Cerebral Palsy Using Wrist Accelerometry. Poster presented during 2008 Annual Meeting in of the Association of Academic Physiatrists.

4. Osorio MB, **Brandys E**, McMahon M, Oleszek JL, Stratton A. Acute Necrotizing Encephalitis: A Multicenter Case Series. Poster presented during 71st Annual Assembly of the American Academy of PMR in 2010. Abstract published in *PM&R-The Journal of Injury, Function and Rehabilitation.* 2010, vol. 2, issue 9S: S138.

Book Chapters

1. Salorio C, **Brandys E**, Morozova O, Pidcock F, Trovato M, Sadowsky C, Christensen J. Neurorehabilitation. Accardo (Ed.), *Capute & Accardo's neurodevelopmental disabilities in infancy and childhood* (3rd ed., 2008). Baltimore, MD: Paul H. Brookes Publishing Company.

2. Christensen J, Trovato M, Salorio C, **Brandys E**, Morozova O, Sadowsky C, Pidcock F. Traumatic Brain Injury. Accardo (Ed.), *Capute & Accardo's neurodevelopmental disabilities in infancy and childhood*, (3rd ed., 2008), Baltimore, MD: Paul H. Brookes Publishing Co.

3. Sadowsky C, Pidcock F, **Brandys E,** Morozova O, Trovato M, Salorio C, Christensen J. Acquired Spinal Cord Dysfunction. Accardo (Ed.), *Capute & Accardo's neurodevelopmental disabilities in infancy and childhood*, (3rd ed., 2008), Baltimore, MD: Paul H. Brookes Publishing Company.

4. Trovato M, Christensen J, Salorio C, **Brandys E**, Sadowsky C, Suskauer S, Pidcock F. Rehabilitation of Children with Critical Illness. In Nichols D. (Ed.), *Rogers Textbook of Pediatric Intensive Care.* (4th ed., 2008), Lippincott Williams & Wilkins.

D. Research Support

None

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2014 *** End Date:** 03/31/2015 **Budget Period** 1

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Burris	R.	Duncan	M.D.	PD/PI	[redacted]	1.80			[redacted]	[redacted]	[redacted]
2.		Chengcheng		Hu	PhD	Biostatitiscian	[redacted]	1.20			[redacted]	[redacted]	[redacted]
3.		Theodore		Trouard	PhD	Co-Investigator	[redacted]	2.20			[redacted]	[redacted]	[redacted]
4.													
5.													
6.													
7.													
8.													
9.	**Total Funds requested for all Senior Key Persons in the attached file**												
												Total Senior/Key Person	[redacted]

Additional Senior Key Persons: Add Attachment Delete Attachment View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	TBD Program Coordinator	12.00			50,000.00	24,350.00	74,350.00
1	IT Specialist	0.24			1,130.00	550.00	1,680.00
2	**Total Number Other Personnel**					**Total Other Personnel**	76,030.00

Total Salary, Wages and Fringe Benefits (A+B) 127,349.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2014 *** End Date:** 03/31/2015 **Budget Period 1**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.	2 professional Camera Kits	35,000.00
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	35,000.00

Additional Equipment: Add Attachment Delete Attachment View Attachment

D. Travel

		Funds Requested ($)
1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	1,260.00
2.	Foreign Travel Costs	
	Total Travel Cost	1,260.00

E. Participant/Trainee Support Costs

		Funds Requested ($)
1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees **Total Participant/Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 1

Next Period

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2014 *** End Date:** 03/31/2015 **Budget Period 1**

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	5,103.00
2. Publication Costs	
3. Consultant Services	11,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	214,110.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8.	
9.	
10.	
Total Other Direct Costs	230,213.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	393,822.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1. MTDC	51.50	194,712.00	100,277.00
2.			
3.			
4.			
Total Indirect Costs			100,277.00

Cognizant Federal Agency DHHS Audit Agency Regional Inspector General for Audit (415) 4

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	494,099.00

J. Fee	Funds Requested ($)

K. * Budget Justification 1239-BudgetJustificationUA.pdf Add Attachment Delete Attachment View Attachment

(Only attach one file.)

OMB Number: 4040-0001
Expiration Date: 06/30/2011

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2015 *** End Date:** 03/31/2016 **Budget Period** 2

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Burris	R.	Duncan	M.D.	PD/PI	[redacted]	1.80			[redacted]	[redacted]	[redacted]
2.		Chengcheng		Hu	PhD	Biostatistician	[redacted]	1.20			[redacted]	[redacted]	[redacted]
3.		Theodore		Trouard	PhD	Co-Investigator	[redacted]	0.24			[redacted]	[redacted]	[redacted]
4.													
5.													
6.													
7.													
8.													

9. **Total Funds requested for all Senior Key Persons in the attached file**

Total Senior/Key Person [redacted]

Additional Senior Key Persons: Add Attachment | Delete Attachment | View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	TBD Project Coordinator	1.00			50,000.00	24,350.00	74,350.00
1	IT Specialist	0.24			1,130.00	550.00	1,680.00
2	**Total Number Other Personnel**					**Total Other Personnel**	76,030.00

Total Salary, Wages and Fringe Benefits (A+B) 115,345.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2015 *** End Date:** 03/31/2016 **Budget Period 2**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	

Additional Equipment: Add Attachment Delete Attachment View Attachment

D. Travel **Funds Requested ($)**

1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	1,260.00
2.	Foreign Travel Costs	
	Total Travel Cost	1,260.00

E. Participant/Trainee Support Costs **Funds Requested ($)**

1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees **Total Participant/Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 2

Next Period

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2015 *** End Date:** 03/31/2016 **Budget Period 2**

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	11,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	365,725.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8.	
9.	
10.	
Total Other Direct Costs	376,725.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	493,330.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1. MTDC	51.50	127,605.00	65,717.00
2.			
3.			
4.			
Total Indirect Costs			65,717.00

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	559,047.00

J. Fee	Funds Requested ($)

K. * Budget Justification 1239-BudgetJustificationUA.pdf Add Attachment Delete Attachment View Attachment

(Only attach one file.)

OMB Number: 4040-0001
Expiration Date: 06/30/2011

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 3

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2016 *** End Date:** 03/31/2017 **Budget Period** 3

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Burris	R.	Duncan	M.D.	PD/PI	[redacted]	1.80			[redacted]	[redacted]	[redacted]
2.		Chengcheng		Hu	PhD	Biostatistician	[redacted]	1.20			[redacted]	[redacted]	[redacted]
3.		Theodore		Trouard	PhD	Co-Investigator	[redacted]	0.24			[redacted]	[redacted]	[redacted]
4.													
5.													
6.													
7.													
8.													

9. **Total Funds requested for all Senior Key Persons in the attached file**

Total Senior/Key Person [redacted]

Additional Senior Key Persons: Add Attachment | Delete Attachment | View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	TBD Project Coordinator	12.00			50,000.00	24,350.00	74,350.00
1	IT Specialist	0.24			1,130.00	550.00	1,680.00
2	**Total Number Other Personnel**					**Total Other Personnel**	76,030.00

Total Salary, Wages and Fringe Benefits (A+B) 115,345.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2016 *** End Date:** 03/31/2017 **Budget Period 3**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	

Additional Equipment: Add Attachment Delete Attachment View Attachment

D. Travel **Funds Requested ($)**

1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	1,260.00
2.	Foreign Travel Costs	
	Total Travel Cost	1,260.00

E. Participant/Trainee Support Costs **Funds Requested ($)**

1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees **Total Participant/Trainee Support Costs**	

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 3

Next Period

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2016 *** End Date:** 03/31/2017 **Budget Period 3**

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	11,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	365,725.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8.	
9.	
10.	
Total Other Direct Costs	376,725.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	493,330.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1. MTDC	51.50	127,605.00	65,717.00
2.			
3.			
4.			
Total Indirect Costs			65,717.00

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	559,047.00

J. Fee	Funds Requested ($)

K. * Budget Justification 1239-BudgetJustificationUA.pdf Add Attachment Delete Attachment View Attachment

(Only attach one file.)

OMB Number: 4040-0001
Expiration Date: 06/30/2011

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 4

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2017 *** End Date:** 03/31/2018 **Budget Period** 4

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Burris	R.	Duncan	M.D.	PD/PI	[redacted]	1.80			[redacted]	[redacted]	[redacted]
2.		Chengcheng		Hu	PhD	Biostatistician	[redacted]	1.20			[redacted]	[redacted]	[redacted]
3.		Theodore		Trouard	PhD	Co-Investigator	[redacted]	0.60			[redacted]	[redacted]	[redacted]
4.													
5.													
6.													
7.													
8.													

9. **Total Funds requested for all Senior Key Persons in the attached file**

Total Senior/Key Person [redacted]

Additional Senior Key Persons: Add Attachment | Delete Attachment | View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	TBD Project Coordinator	12.00			50,000.00	24,350.00	74,350.00
1	TBD Graduate Student	3.00			7,233.00	4,701.00	11,934.00
1	IT Specialist	0.24			1,130.00	550.00	1,680.00
3	**Total Number Other Personnel**					**Total Other Personnel**	87,964.00

Total Salary, Wages and Fringe Benefits (A+B) 131,780.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2017 *** End Date:** 03/31/2018 **Budget Period 4**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	Total funds requested for all equipment listed in the attached file	
	Total Equipment	

Additional Equipment: Add Attachment Delete Attachment View Attachment

D. Travel **Funds Requested ($)**

1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	1,260.00
2.	Foreign Travel Costs	
	Total Travel Cost	1,260.00

E. Participant/Trainee Support Costs **Funds Requested ($)**

1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees	Total Participant/Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 4

Next Period

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2017 *** End Date:** 03/31/2018 **Budget Period 4**

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	11,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	365,725.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8.	
9.	
10.	
Total Other Direct Costs	376,725.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	509,765.00

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1. MTDC	51.50	139,823.00	72,009.00
2.			
3.			
4.			
Total Indirect Costs			72,009.00

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	581,774.00

J. Fee	Funds Requested ($)

K. * Budget Justification 1239-BudgetJustificationUA.pdf Add Attachment Delete Attachment View Attachment

(Only attach one file.)

OMB Number: 4040-0001
Expiration Date: 06/30/2011

Previous Period

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 5

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2018 *** End Date:** 03/31/2019 **Budget Period** 5

A. Senior/Key Person

	Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.		Burris	R.	Duncan	M.D.	PD/PI	[redacted]	1.80			[redacted]	[redacted]	[redacted]
2.		Chengcheng		Hu	PhD	Biostatistician	[redacted]	1.20			[redacted]	[redacted]	[redacted]
3.		Theodore		Trouard	PhD	Co-Investigator	[redacted]	0.60			[redacted]	[redacted]	[redacted]
4.													
5.													
6.													
7.													
8.													

9. **Total Funds requested for all Senior Key Persons in the attached file**

Total Senior/Key Person [redacted]

Additional Senior Key Persons: Add Attachment | Delete Attachment | View Attachment

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	TBD Project Coordinator	12.00			50,000.00	24,350.00	74,350.00
1	TBD Graduate Assistant	3.00			7,233.00	4,701.00	11,934.00
1	IT Specialist	0.24			1,130.00	550.00	1,680.00
3	**Total Number Other Personnel**					**Total Other Personnel**	87,964.00

Total Salary, Wages and Fringe Benefits (A+B) 131,780.00

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 5

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2018 *** End Date:** 03/31/2019 **Budget Period 5**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

	Equipment item	* Funds Requested ($)
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		
11.	**Total funds requested for all equipment listed in the attached file**	
	Total Equipment	

Additional Equipment: Add Attachment Delete Attachment View Attachment

D. Travel		**Funds Requested ($)**
1.	Domestic Travel Costs (Incl. Canada, Mexico and U.S. Possessions)	8,760.00
2.	Foreign Travel Costs	
	Total Travel Cost	8,760.00

E. Participant/Trainee Support Costs		**Funds Requested ($)**
1.	Tuition/Fees/Health Insurance	
2.	Stipends	
3.	Travel	
4.	Subsistence	
5.	Other	
	Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION F-K, BUDGET PERIOD 5

*** ORGANIZATIONAL DUNS:** 8063456170000

*** Budget Type:** ☒ Project ☐ Subaward/Consortium

Enter name of Organization: Arizona Board of Regents, Unive

Delete Entry *** Start Date:** 04/01/2018 *** End Date:** 03/31/2019 **Budget Period 5**

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	11,000.00
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	273,990.00
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8.	
9.	
10.	
Total Other Direct Costs	284,990.00

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	425,530.00

H. Indirect Costs

	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1.	MTDS	51.50	147,323.00	75,871.00
2.				
3.				
4.				
	Total Indirect Costs			75,871.00

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	501,401.00

J. Fee	Funds Requested ($)

K. * Budget Justification 1239-BudgetJustificationUA.pdf Add Attachment Delete Attachment View Attachment

(Only attach one file.)

4.4 Budget Justification

Arizona Health Sciences Center, Tucson, Arizona

PERSONNEL

Duncan, Burris, MD, Professor Emeritus, formerly Professor of Pediatrics & Public Health
Institutional Affiliation: University of Arizona, Health Sciences Center, Mel & Enid Zuckerman College of Public Health (COPH)
Role on the project: Principal Investigator 1.8 months' per year in all five years. One of my chief responsibilities is to insure that the research is conducted in a way that respects the rights and safety of all enrolled participants and is in accordance with the institutional policies of the State and the University of Arizona. It is my job to supervise the study personnel making sure that those hired are qualified to perform the tasks they are assigned, that they have a clear understanding of the project, that they adhere to the study protocol, that they realize the importance of immediately reporting any adverse or unanticipated problems, and that they respect the confidentiality of the families enrolled. I am the direct liaison to the Data and Safety Monitoring Board and will keep the Board informed as to the progress of the study and when and if any adverse problems arise. I am responsible for ensuring that no child begins an evaluation or enters therapy until the consent has been signed and that the randomization and stratification is conducted as planned. I will supervise the Project Coordinator in Tucson who will oversee all data collection; will initiate frequent telephone interactions with the enrolled families; will schedule the evaluations; coordinate the scoring therapists, and will assist the biostatistician in compiling the data. It is my responsibility to write and submit annual reports and be intimately involved with any and all manuscripts that emanate from this project.

Hu, Chengcheng, PhD, Associate Professor of Public Health
Institutional Affiliation: University of Arizona Health Sciences Center, (COPH)
Role on the Project: Biostatistician 1.2 months' effort each year for all five years
Dr. Hu has assisted with the methodological aspects of this investigation and will provide biostatistician expertise and experience to the grant.

Project Coordinator: 12 months' effort each year in all five years He/she will be responsible for overseeing each detail of the study at both sites.

- Receiving the call from the referring child provider and then the call from the child's parent
- Explaining the study protocol to the parent and if the parent is still interested, meet with the parent and go over the parental consent form in detail, answer any questions, and if the parent agrees to enroll his/her child in the study, witness the signature and sign it
- Obtain the child's age and level of severity and inform the biostatistician who will randomize the child one of the two groups

- Inform Fragomeni, Mary Lou, MS, CCC-SLP Speech Language Pathologist and Manager of Outpatient Pediatric Therapies Department at the Tucson Medical Center of the enrollment and then give the parent a written schedule outlining when the therapies will begin and the schedule of therapies and recording of the evaluations the child will follow
- Bi-weekly phone calls to the parent to listen to how the child is doing and to serve as a reminder of the therapies and evaluations. Notes will be made of the conversations
- Collect and deliver the DVD evaluations to the scoring therapists
- The Tucson coordinator will have the ultimate responsibility of the password protected web site and will check it at least 3 times each week to insure that the treating and evaluation therapists in both Tucson and Phoenix are keeping current with data entry and that the data entered is 'clean'
- Assist in the analysis of the data
- Assist in the writing of the manuscripts that will come from the study

Trouard, Theodore, PhD, Associate Professor, Biomedical Engineering and Medical Imaging, Assistant
Direct, BI05 Institute.
Institutional Affiliation: U of AZ, Arizona Health Sciences Center, Dept. of Biomedical Engineering
Role on the Project: Co-Investigator Overseeing the imaging activities of the subset of children (1.2, 0.24, 0.24, 0.6 and 0.6 months' effort in years 1-5, respectively). Dr. Trouard has many years of experience in the development, application and analysis of MRI in neurological disorders. He will be responsible for overseeing all imaging activities in the exploratory aim including coordination of image acquisition with Phoenix Children's Hospital, ensuring the quality of image data acquisition, transfer of imaging data to the University of Arizona, analysis of images and interpretation of results. He will directly supervise the graduate student who will work on image analysis in years 4 and 5 of the project.

Graduate Research Assistant, TBD 3 months' effort in years 4 and 5 (25% salary requested). The student will be responsible for analysis of 3D T1-wieghted, DTI and FLAIR images. The graduate student will be recruited from the Biomedical Engineering Graduate Interdisciplinary Program, of which Dr. Trouard is a faculty member. Dr. Trouard has recruited many PhD and MS students into his lab from the BME GIDP and has trained them in MRI acquisition and analysis techniques.

Holister, Jason
Institutional Affiliation: U of AZ Health Sciences Center, COPH
Role on the Project: IT specialist. 0.24 CM effort for all five years of the project. IT support in the College of Public Health

CONSULTANT COSTS
Scoring of the Evaluation instrument: $44,000 requested. The GMFM-66 that will be administered by the treating therapist will be video-taped and then scored by a 'blinded' therapist. It is estimated that each evaluation will take the scoring therapist approximately 1½ hours. The budget has allotted $80/evaluation. The reimbursement for the scoring will be 5 evaluations x $80 x 110 children = $44,000. This has been spread appropriately over the 5-year grant period.

EQUIPMENT
$35,000 requested. Sim Capture at the Phoenix Children's Hospital and the Tucson Medical Center): Capturing the way a child responds to the skills/functions on the GMFM-66 he/she is asked to preform is crucial to securing an accurate evaluation of efficacy of this therapeutic approach. The SimCapture ultraportable camera and computer combination will be purchased from B-Line Medical. These units are flexible and portable with high resolution images. The unit allows the distribution of the recorded images directly to the password protected web site designated for this project.

We got an estimate from the sim lab here in Tucson for a 2-camera setup that is fairly well self-contained, meaning you could change locations much easier. That will be the cost of two 'client' units, plus the server we would need to maintain down in Tucson, is around $35k total.

Lap top computer x2: $2,600 requested - The project coordinator at each site will need a computer to keep files, to enter data directly onto the pass word protected web site, and help with the analysis of the data. The project coordinator in Tucson will carry the computer from her office at the COPH to both of the other sites, the Tucson Medical Center and the Phoenix Children's Hospital.

SUPPLIES
$2,503 requested. Evaluation instruments include the Gross Motor Function Measure-66 (GMFM) and the Pediatric Evaluation of Disability Inventory (PEDI). Seven GMFM manuals are needed, one for each site and one for each of the five scoring therapists (unit cost of $112.95 for a cost of $790.65). Two PEDI manuals are needed, one for each site and will be used by the Project Coordinators (unit cost of $125.95 for a cost of $251.90). Five scoring sheets for the GMFM will be needed for each of the 110 children (550 scoring sheets) in the study (unit cost of $0.83 for a cost of $456.50). Five scoring sheets for the PEDI will be needed for each of the 110 children (550 scoring sheets) in the study (unit cost of $1.824 for a cost of $1003.20). Total cost for evaluation supplies is $2502.25.

TRAVEL

$13,800 requested. It is anticipated that three of the investigators at the University of Arizona will either attend or present the findings of this study at a national conference. We have allotted $2,500 for each of these individuals in the last year of the grant for a total cost of $7,500.

The PI and/or the Tucson Coordinator will travel to Phoenix a minimum of once each month during the entire 5-year study. That would be a total of 60 round trips between Tucson and Phoenix
(235 miles) = 6,195 miles @ $0.445/mile = $6,300.

OTHER EXPENSES

$11,000 requested. Ten thousand dollars has been allocated for construction and maintenance of the password protected web site. The funds will be spent in the first year when the web site will be developed and the data collection forms will be converted to a web site format.

One thousand dollars has been allocated for an orientation conference to be held during the first six months of the grant. The conference will convene at the Phoenix Children's Hospital with attendance by the treating therapists from Phoenix and Tucson. At this time, an overview of the investigation will be given and an instructor of the Perception Action approach to physical therapy will be there to insure that the therapists at both sites will be administering therapies in the same way and will answer any question the therapists might have.

RESEARCH & RELATED BUDGET - Cumulative Budget

		Totals ($)
Section A, Senior/Key Person		217,581.00
Section B, Other Personnel		404,018.00
Total Number Other Personnel	12	
Total Salary, Wages and Fringe Benefits (A+B)		621,599.00
Section C, Equipment		35,000.00
Section D, Travel		13,800.00
1. Domestic	13,800.00	
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		1,645,378.00
1. Materials and Supplies	5,103.00	
2. Publication Costs		
3. Consultant Services	55,000.00	
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs	1,585,275.00	
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1		
9. Other 2		
10. Other 3		
Section G, Direct Costs (A thru F)		2,315,777.00
Section H, Indirect Costs		379,591.00
Section I, Total Direct and Indirect Costs (G + H)		2,695,368.00
Section J, Fee		

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2014 *** End Date:** 03-31-2015 **Budget Period: 1**

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.	Jorge		Arango	MD	Co-PI	91,464.00	1.20			9,146.00	2,067.00	11,213.00
2.	Ewa		Brandys	MD	Co-Investigator	179,700.00	1.20			17,970.00	4,061.00	22,031.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Mime Type: **Total Senior/Key Person** **33,244.00**

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	TBN - Program Coordinator	4.80			24,000.00	5,424.00	29,424.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**29,424.00**
					Total Salary, Wages and Fringe Benefits (A+B)		**62,668.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2014 *** End Date:** 03-31-2015 **Budget Period: 1**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
	Equipment Item	*** Funds Requested ($)**
Total funds requested for all equipment listed in the attached file		
	Total Equipment	
Additional Equipment:	File Name:	Mime Type:

D. Travel	**Funds Requested ($)**
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	1,000.00
2. Foreign Travel Costs	
Total Travel Cost	**1,000.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)**
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2014 *** End Date:** 03-31-2015 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Therapy	70,080.00
9. Evaluations and MRI/DTI	8,840.00
10. Orientation Conference	1,500.00
Total Other Direct Costs	**80,420.00**

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	**144,088.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1. MTDC	55.00	65,168.00	35,842.00
		Total Indirect Costs	**35,842.00**

Cognizant Federal Agency DHHS, Helen Fung, 415-437-7820

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	**179,930.00**

J. Fee	Funds Requested ($)

K. * Budget Justification File Name: 1252-BudgetJustificationPhoenix.pdf Mime Type: application/pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2015 *** End Date:** 03-31-2016 **Budget Period: 2**

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.	Jorge		Arango	MD	Co-PI	91,464.00	1.20			9,146.00	2,067.00	11,213.00
2.	Ewa		Brandys	MD	Co-Investigator	179,700.00	1.20			17,970.00	4,061.00	22,031.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Mime Type: **Total Senior/Key Person** **33,244.00**

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	TBN - Program Coordinator	4.80			24,000.00	5,424.00	29,424.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**29,424.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**62,668.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Tracking Number: GRANT11413275

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2015 *** End Date:** 03-31-2016 **Budget Period: 2**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
	Equipment Item	*** Funds Requested ($)**
Total funds requested for all equipment listed in the attached file		
	Total Equipment	
Additional Equipment:	File Name:	Mime Type:

D. Travel	**Funds Requested ($)**
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	1,000.00
2. Foreign Travel Costs	
Total Travel Cost	**1,000.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)**
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2015 *** End Date:** 03-31-2016 **Budget Period: 2**

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Therapy	175,200.00
9. Evaluations	9,600.00
10. MRI/DTI	15,000.00
Total Other Direct Costs	**199,800.00**

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	**263,468.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1. MTDC	55.00	63,668.00	35,017.00
		Total Indirect Costs	**35,017.00**

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	**298,485.00**

J. Fee	Funds Requested ($)

K. * Budget Justification File Name: 1252-BudgetJustificationPhoenix.pdf Mime Type: application/pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 3

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2016 *** End Date:** 03-31-2017 **Budget Period: 3**

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.	Jorge		Arango	MD	Co-PI	91,464.00	1.20			9,146.00	2,067.00	11,213.00
2.	Ewa		Brandys	MD	Co-Investigator	179,700.00	1.20			17,970.00	4,061.00	22,031.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Mime Type: **Total Senior/Key Person** **33,244.00**

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	TBN - Program Coordinator	4.80			24,000.00	5,424.00	29,424.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**29,424.00**
					Total Salary, Wages and Fringe Benefits (A+B)		**62,668.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Tracking Number: GRANT11413275

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2016 *** End Date:** 03-31-2017 **Budget Period: 3**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	* Funds Requested ($)
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name: Mime Type:

D. Travel	Funds Requested ($)
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	1,000.00
2. Foreign Travel Costs	
Total Travel Cost	**1,000.00**

E. Participant/Trainee Support Costs	Funds Requested ($)
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 3

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2016 *** End Date:** 03-31-2017 **Budget Period: 3**

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Therapy	175,200.00
9. Evaluations	9,600.00
10. MRI/DTI	15,000.00
Total Other Direct Costs	**199,800.00**

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	**263,468.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1. MTDC	55.00	63,668.00	35,017.00
		Total Indirect Costs	**35,017.00**

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	**298,485.00**

J. Fee	Funds Requested ($)

K. * Budget Justification File Name: 1252-BudgetJustificationPhoenix.pdf Mime Type: application/pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 4

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2017 *** End Date:** 03-31-2018 **Budget Period: 4**

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.	Jorge		Arango	MD	Co-PI	91,464.00	1.20			9,146.00	2,067.00	11,213.00
2.	Ewa		Brandys	MD	Co-Investigator	179,700.00	1.20			17,970.00	4,061.00	22,031.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Mime Type: **Total Senior/Key Person** **33,244.00**

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	TBN - Program Coordinator	4.80			24,000.00	5,424.00	29,424.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**29,424.00**
					Total Salary, Wages and Fringe Benefits (A+B)		**62,668.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2017 *** End Date:** 03-31-2018 **Budget Period: 4**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	* Funds Requested ($)
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name: Mime Type:

D. Travel	Funds Requested ($)
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	1,000.00
2. Foreign Travel Costs	
Total Travel Cost	**1,000.00**

E. Participant/Trainee Support Costs	Funds Requested ($)
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 4

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2017 *** End Date:** 03-31-2018 **Budget Period: 4**

F. Other Direct Costs		**Funds Requested ($)**
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Therapy		175,200.00
9. Evaluations		9,600.00
10. MRI/DTI		15,000.00
	Total Other Direct Costs	**199,800.00**

G. Direct Costs		**Funds Requested ($)**
	Total Direct Costs (A thru F)	**263,468.00**

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	*** Funds Requested ($)**
1. MTDC	55.00	63,668.00	35,017.00
		Total Indirect Costs	**35,017.00**

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs		**Funds Requested ($)**
	Total Direct and Indirect Institutional Costs (G + H)	**298,485.00**

J. Fee	**Funds Requested ($)**

K. * Budget Justification File Name: 1252-BudgetJustificationPhoenix.pdf Mime Type: application/pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 5

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2018 *** End Date:** 03-31-2019 **Budget Period: 5**

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.	Jorge		Arango	MD	Co-PI	91,464.00	1.20			9,146.00	2,067.00	11,213.00
2.	Ewa		Brandys	MD	Co-Investigator	179,700.00	1.20			17,970.00	4,061.00	22,031.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Mime Type: **Total Senior/Key Person** **33,244.00**

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	TBN - Program Coordinator	4.80			24,000.00	5,424.00	29,424.00
1	**Total Number Other Personnel**					**Total Other Personnel**	**29,424.00**
						Total Salary, Wages and Fringe Benefits (A+B)	**62,668.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Tracking Number: GRANT11413275

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 5

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2018 *** End Date:** 03-31-2019 **Budget Period: 5**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	* Funds Requested ($)

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name: Mime Type:

D. Travel	Funds Requested ($)
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	8,500.00
2. Foreign Travel Costs	
Total Travel Cost	**8,500.00**

E. Participant/Trainee Support Costs	Funds Requested ($)
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	

Number of Participants/Trainees **Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 5

*** ORGANIZATIONAL DUNS:** 1104435950000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Phoenix Children's Hospital

*** Start Date:** 04-01-2018 *** End Date:** 03-31-2019 **Budget Period: 5**

F. Other Direct Costs	**Funds Requested ($)**
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Therapy	105,120.00
9. Evaluations	5,760.00
Total Other Direct Costs	**110,880.00**

G. Direct Costs	**Funds Requested ($)**
Total Direct Costs (A thru F)	**182,048.00**

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	*** Funds Requested ($)**
1. MTDC	55.00	71,168.00	39,142.00
		Total Indirect Costs	**39,142.00**

Cognizant Federal Agency

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	**Funds Requested ($)**
Total Direct and Indirect Institutional Costs (G + H)	**221,190.00**

J. Fee	**Funds Requested ($)**

K. * Budget Justification File Name: 1252-BudgetJustificationPhoenix.pdf Mime Type: application/pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		**166,220.00**
Section B, Other Personnel		**147,120.00**
Total Number Other Personnel	5	
Total Salary, Wages and Fringe Benefits (A+B)		**313,340.00**
Section C, Equipment		
Section D, Travel		**12,500.00**
1. Domestic	12,500.00	
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		**790,700.00**
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	700,800.00	
9. Other 2	43,400.00	
10. Other 3	46,500.00	
Section G, Direct Costs (A thru F)		**1,116,540.00**
Section H, Indirect Costs		**180,035.00**
Section I, Total Direct and Indirect Costs (G + H)		**1,296,575.00**
Section J, Fee		

Budget Justification

Phoenix Children's Hospital, Phoenix, Arizona

PERSONNEL

Arango, Jorge, MD, Research Scientist, Children's Neuroscience Research

Institutional Affiliation: Barrow Neurological Institute at Phoenix Children's Hospital, Phoenix, AZ

Role on the Project: Co-PI 1.2 months' effort each year for all five years

As Co-PI he will assist the PI in overseeing the entire project and making sure it is done with scientific scrutiny and integrity. His role in Phoenix is the implementation and oversight of all study activities performed at PCH along with the continuous evaluation of study findings. He will assist with the analyzes of the results of the investigation and writing of manuscripts that emanate from the findings.

Brandys, Ewa, MD, Division Chief, Pediatric Rehabilitation Medicine, Medical Director of Rehabilitation Services

Institutional Affiliation: Barrow Neurological Institute at Phoenix Children's Hospital, Phoenix, AZ

Role on the Project: Co-Investigator 1.2 months' effort each year for all five years

Dr. Brandys will have the responsibility of coordinating and overseeing the rehabilitation therapies at both sites, Phoenix Children's Hospital and the Tucson Medical Center. She is located at the PCH and her effort will involve frequent on-site visits to the Tucson location.

Project Coordinator: 0.8 months' effort each year in all five years. He/she will be responsible for overseeing each detail of the study in Phoenix

- Receiving the call from the referring child provider and then the call from the child's parent
- Explaining the study protocol to the parent and if the parent is still interested, meet with the parent and go over the parental consent form in detail, answer any questions, and if the parent agrees to enroll his/her child in the study, witness the signature and sign it
- Obtain the child's age and level of severity and inform the biostatistician who will randomize the child one of the two groups
- Inform Dr. Brandys of the enrollment and then give the parent a written schedule outlining when the therapies will begin and the schedule of therapies and recording of the evaluations the child will follow
- Bi-weekly phone calls to the parent to listen to how the child is doing and to serve as a reminder of the therapies and evaluations – notes will be made of the conversations
- Collect and deliver the DVD evaluations to the scoring therapists
- The Tucson coordinator will have the ultimate responsibility of the password protected web site but the Phoenix coordinator will check the web site at least 3 times each week to insure that the treating and evaluation therapists in Phoenix are keeping current with data entry and that the data entered is 'clean'

TRAVEL

$13,700 requested - It is anticipated that three of the investigators at the Phoenix Children's Hospital will either attend or present the findings of this study at a national conference. We have allotted $2,500 for each of these individuals in the last year of the grant for a total cost of $7,500.

It is anticipated that Dr. Brandys will travel from Phoenix to Tucson once each month. The round trip covers 232 miles and a rate of $0.445/ mile = $103.24 x 12 times each year = $1,240 x 5 years = $6,200.

OUT PATIENT CARE:

$789,200 requested - Physical and Occupational Therapies: During the 48-week protocol, each child enrolled in Tucson (30) will have 96 therapy sessions of 30 minutes each by the Physical Therapists and 96 therapy sessions of 30 minutes each by the Occupational Therapist. Five of the sessions of physical therapy will be evaluation sessions and first encounter with the Occupational Therapist will be an evaluation session. It is estimated that at least 20 sessions will be reimbursed by the family's insurance company. That number is purely an estimate as it is recognized that some families will not have insurance coverage and some insurance companies will cover more than 20 therapies over this time period. That leaves a total of 146 therapies (71 PT and 75 OT) x $60 per session x 80 children = $700,800. This has been spread over the 5-year grant period knowing that no children will be enrolled during the first 6 months of the first year when the study is being set up. The last child will be enrolled so the therapy session will terminate three months prior to the end of the grant period. The last three months have been left for performing the analysis and writing the manuscripts.

Administration of the GMFM-66 evaluation instrument by the treating therapists: The GMFM-66 will be administered five times to each child during the 48-week protocol (baseline and then every 12 weeks). Insurance should pay for the first evaluation and each follow-up evaluation will be reimbursed $120. The cost of administering the evaluation: 4 evaluations x $120 per evaluation x 80 children = $38,400. This has been distributed appropriately over the 5-year grant period.

To insure standardization of the MRI/DTI examinations, all will be done with the same equipment at the Barrow Neurological Institute at Phoenix Children's Hospital. Each of the children in this subset (20) will have two such radiologic examinations. The cost of radiographic procedure is $650 per examination. Since all the subjects (20) in this subset will be quite young, they will have to have anesthesia and an anesthesiologist must be in attendance at a charge of $600 per examination. Thus the total cost for this portion of the investigation will be 20 (children) x 2 (examinations) x [$650 (procedure price) + $600 (anesthesia)] = $50,000.

OTHER EXPENCES:

$6,500 requested - One thousand dollars has been allocated each year for training of the physical and occupational therapists. Such training is important for them to enhance and update their skills.

Five hundred dollars has been allocated to reimburse salary support for each of three therapists from Phoenix Children's Hospital to attend an orientation conference that will be held during the first six months of the grant. The conference will convene at the Phoenix Children's Hospital with attendance by the treating therapists from Phoenix and Tucson. At this time, an overview of the investigation will be given by Drs. Duncan, Brandys, and Arango. An instructor of the Perception Action approach to physical therapy will be there to insure that the therapists at both sites will be administering therapies in the same way and will answer any question the therapists might have.

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2014 *** End Date:** 03-31-2015 **Budget Period: 1**

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.	Marylou		Fragomeni		Head Ped. Therapist		0.01			0.00	0.00	0.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Mime Type: **Total Senior/Key Person** **0.00**

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	**0.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Tracking Number: GRANT11413275

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2014 *** End Date:** 03-31-2015 **Budget Period: 1**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	*** Funds Requested ($)**
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name: Mime Type:

D. Travel	**Funds Requested ($)**
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs	**Funds Requested ($)**
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 1

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2014 *** End Date:** 03-31-2015 **Budget Period: 1**

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Therapy and Evaluations	31,680.00
9. Training/Education	1,000.00
10. Orientation Conference	1,500.00
Total Other Direct Costs	**34,180.00**

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	**34,180.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
1. MTDC	0.00	2,500.00	0.00
		Total Indirect Costs	**0.00**

Cognizant Federal Agency Jim Olson Phone 701-277-2298

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	**34,180.00**

J. Fee	Funds Requested ($)

K. * Budget Justification File Name: 1253-BudgetJustificationTMC.pdf Mime Type: application/pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2015 *** End Date:** 03-31-2016 **Budget Period: 2**

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.	Marylou		Fragomeni		Head Ped. Therapist		0.01			0.00	0.00	0.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Mime Type: **Total Senior/Key Person** **0.00**

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	**0.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2015 *** End Date:** 03-31-2016 **Budget Period: 2**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	*** Funds Requested ($)**
Total funds requested for all equipment listed in the attached file	
Total Equipment	

Additional Equipment: File Name: Mime Type:

D. Travel	**Funds Requested ($)**
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs	**Funds Requested ($)**
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 2

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2015 *** End Date:** 03-31-2016 **Budget Period: 2**

F. Other Direct Costs	**Funds Requested ($)**
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Therapy	62,640.00
9. Orientation Conference	3,600.00
10. Training Education	1,000.00
Total Other Direct Costs	**67,240.00**

G. Direct Costs	**Funds Requested ($)**
Total Direct Costs (A thru F)	**67,240.00**

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	*** Funds Requested ($)**
		Total Indirect Costs	

Cognizant Federal Agency Jim Olson - Phone 701-277-2298

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	**Funds Requested ($)**
Total Direct and Indirect Institutional Costs (G + H)	**67,240.00**

J. Fee	**Funds Requested ($)**

K. * Budget Justification File Name: 1253-BudgetJustificationTMC.pdf Mime Type: application/pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 3

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2016 *** End Date:** 03-31-2017 **Budget Period: 3**

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.	Marylou		Fragomeni		Head Ped. Therapist		0.01			0.00	0.00	0.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Mime Type: **Total Senior/Key Person** **0.00**

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	**0.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 3

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2016 *** End Date:** 03-31-2017 **Budget Period: 3**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	* Funds Requested ($)
Total funds requested for all equipment listed in the attached file	
	Total Equipment

Additional Equipment: File Name: Mime Type:

D. Travel **Funds Requested ($)**

1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)
2. Foreign Travel Costs

Total Travel Cost

E. Participant/Trainee Support Costs **Funds Requested ($)**

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees **Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 3

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2016 *** End Date:** 03-31-2017 **Budget Period: 3**

F. Other Direct Costs	**Funds Requested ($)**
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Therapy	62,640.00
9. Evaluations	3,600.00
10. Training/Education	1,000.00
Total Other Direct Costs	**67,240.00**

G. Direct Costs	**Funds Requested ($)**
Total Direct Costs (A thru F)	**67,240.00**

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	*** Funds Requested ($)**
		Total Indirect Costs	

Cognizant Federal Agency Jim Olson - Phone 701-277-2298

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	**Funds Requested ($)**
Total Direct and Indirect Institutional Costs (G + H)	**67,240.00**

J. Fee	**Funds Requested ($)**

K. * Budget Justification File Name: 1253-BudgetJustificationTMC.pdf Mime Type: application/pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 4

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2017 *** End Date:** 03-31-2018 **Budget Period: 4**

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.	Marylou		Fragomeni		Head Ped. Therapist		0.01			0.00	0.00	0.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Mime Type: **Total Senior/Key Person** **0.00**

B. Other Personnel

* Number of Personnel		* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits	* Funds Requested ($)
	Post Doctoral Associates							
	Graduate Students							
	Undergraduate Students							
	Secretarial/Clerical							
0	**Total Number Other Personnel**						**Total Other Personnel**	

Total Salary, Wages and Fringe Benefits (A+B) **0.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

Tracking Number: GRANT11413275

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 4

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2017 *** End Date:** 03-31-2018 **Budget Period: 4**

C. Equipment Description

List items and dollar amount for each item exceeding $5,000

Equipment Item	* Funds Requested ($)

Total funds requested for all equipment listed in the attached file

Total Equipment

Additional Equipment: File Name: Mime Type:

D. Travel	Funds Requested ($)
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	
2. Foreign Travel Costs	
Total Travel Cost	

E. Participant/Trainee Support Costs	Funds Requested ($)
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 4

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2017 *** End Date:** 03-31-2018 **Budget Period: 4**

F. Other Direct Costs	**Funds Requested ($)**
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Therapy	62,640.00
9. Evaluations	3,600.00
10. Training and Education	1,000.00
Total Other Direct Costs	**67,240.00**

G. Direct Costs	**Funds Requested ($)**
Total Direct Costs (A thru F)	**67,240.00**

H. Indirect Costs

Indirect Cost Type	**Indirect Cost Rate (%)**	**Indirect Cost Base ($)**	*** Funds Requested ($)**
		Total Indirect Costs	

Cognizant Federal Agency Jim Olson - Phone 277-2298

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	**Funds Requested ($)**
Total Direct and Indirect Institutional Costs (G + H)	**67,240.00**

J. Fee	**Funds Requested ($)**

K. * Budget Justification File Name: 1253-BudgetJustificationTMC.pdf Mime Type: application/pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION A & B, BUDGET PERIOD 5

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2018 *** End Date:** 03-31-2019 **Budget Period: 5**

A. Senior/Key Person

Prefix	* First Name	Middle Name	* Last Name	Suffix	* Project Role	Base Salary ($)	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits ($)	* Funds Requested ($)
1.	Marylou		Fragomeni		Head Ped. Therapist		0.01			0.00	0.00	0.00

Total Funds Requested for all Senior Key Persons in the attached file

Additional Senior Key Persons: File Name: Mime Type: **Total Senior/Key Person** **0.00**

B. Other Personnel

* Number of Personnel	* Project Role	Cal. Months	Acad. Months	Sum. Months	* Requested Salary ($)	* Fringe Benefits	* Funds Requested ($)
	Post Doctoral Associates						
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
0	**Total Number Other Personnel**					**Total Other Personnel**	
						Total Salary, Wages and Fringe Benefits (A+B)	**0.00**

RESEARCH & RELATED Budget {A-B} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTION C, D, & E, BUDGET PERIOD 5

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2018 *** End Date:** 03-31-2019 **Budget Period: 5**

C. Equipment Description		
List items and dollar amount for each item exceeding $5,000		
	Equipment Item	*** Funds Requested ($)**
Total funds requested for all equipment listed in the attached file		
	Total Equipment	
Additional Equipment:	File Name:	Mime Type:

D. Travel	**Funds Requested ($)**
1. Domestic Travel Costs (Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	
Total Travel Cost	**5,000.00**

E. Participant/Trainee Support Costs	**Funds Requested ($)**
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	**Total Participant/Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

RESEARCH & RELATED BUDGET - SECTIONS F-K, BUDGET PERIOD 5

*** ORGANIZATIONAL DUNS:** 0069027120000

*** Budget Type:** ❍ Project ● Subaward/Consortium

Enter name of Organization: Tucson Medical Center

*** Start Date:** 04-01-2018 *** End Date:** 03-31-2019 **Budget Period: 5**

F. Other Direct Costs	Funds Requested ($)
1. Materials and Supplies	
2. Publication Costs	
3. Consultant Services	
4. ADP/Computer Services	
5. Subawards/Consortium/Contractual Costs	
6. Equipment or Facility Rental/User Fees	
7. Alterations and Renovations	
8. Therapy	44,640.00
9. Evaluations	2,160.00
10. Training and Education	1,000.00
Total Other Direct Costs	**47,800.00**

G. Direct Costs	Funds Requested ($)
Total Direct Costs (A thru F)	**52,800.00**

H. Indirect Costs

Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base ($)	* Funds Requested ($)
		Total Indirect Costs	

Cognizant Federal Agency Jim Olson - Phone 701-277-2298

(Agency Name, POC Name, and POC Phone Number)

I. Total Direct and Indirect Costs	Funds Requested ($)
Total Direct and Indirect Institutional Costs (G + H)	**52,800.00**

J. Fee	Funds Requested ($)

K. * Budget Justification File Name: 1253-BudgetJustificationTMC.pdf Mime Type: application/pdf

(Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals ($)	
Section A, Senior/Key Person		**0.00**
Section B, Other Personnel		
Total Number Other Personnel		
Total Salary, Wages and Fringe Benefits (A+B)		**0.00**
Section C, Equipment		
Section D, Travel		**5,000.00**
1. Domestic	5,000.00	
2. Foreign		
Section E, Participant/Trainee Support Costs		
1. Tuition/Fees/Health Insurance		
2. Stipends		
3. Travel		
4. Subsistence		
5. Other		
6. Number of Participants/Trainees		
Section F, Other Direct Costs		**283,700.00**
1. Materials and Supplies		
2. Publication Costs		
3. Consultant Services		
4. ADP/Computer Services		
5. Subawards/Consortium/Contractual Costs		
6. Equipment or Facility Rental/User Fees		
7. Alterations and Renovations		
8. Other 1	264,240.00	
9. Other 2	13,960.00	
10. Other 3	5,500.00	
Section G, Direct Costs (A thru F)		**288,700.00**
Section H, Indirect Costs		**0.00**
Section I, Total Direct and Indirect Costs (G + H)		**288,700.00**
Section J, Fee		

Budget Justification

Tucson Medical Center, Tucson, Arizona

TRAVEL
$5,000 requested - It is anticipated that two of the therapists at the Tucson Medical Center will either attend or present the findings of this study at a national conference. We have allotted $2,500 for each of these individuals in the last year of the grant for a total cost of $5,000.

OUT PATIENT CARE
$277,200 requested - Physical and Occupational Therapies: During the 48-week protocol, each child enrolled in Tucson (30) will have 96 therapy sessions of 30 minutes each by the Physical Therapists and 96 therapy sessions of 30 minutes each by the Occupational Therapist. Five of the sessions of physical therapy will be evaluation sessions and first encounter with the Occupational Therapist will be an evaluation session. It is estimated that at least 20 sessions will be reimbursed by the family's insurance company. That number is purely an estimate as it is recognized that some families will not have insurance coverage and some insurance companies will cover more than 20 therapies over this time period. That leaves a total of 146 therapies (71 PT and 75 OT) x $60 per session x 30 children = $262,800. This has been spread over the 5-year grant period knowing that no children will be enrolled during the first 6 months of the first year when the study is being set up. The last child will be enrolled so the therapy session will terminate three months prior to the end of the grant period. The last three months have been left for performing the analysis and writing the manuscripts.

Administration of the GMFM-66 evaluation instrument by the treating therapists: The GMFM-66 will be administered five times to each child during the 48-week protocol (baseline and then every 12 weeks). Insurance should pay for the first evaluation and each follow-up evaluation will be reimbursed $120. The cost of administering the evaluation: 4 evaluations x $120 per evaluation x 30 children = $14,400. This has been distributed appropriately over the 5-year grant period.

OTHER EXPENSES
$6,500 requested - One thousand dollars has been allocated each year for training of the physical and occupational therapists. Such training is important for them to enhance and update their skills.

Fifteen hundred dollars has been allocated to reimburse salary support of three therapists from Tucson to attend an orientation conference that will be held during the first six months of the grant. The conference will convene at the Phoenix Children's Hospital with attendance by the treating therapists from Phoenix and Tucson. At this time, an overview of the investigation will be given by Drs. Duncan, Brandys, and Arango. An instructor of the Perception Action approach to physical therapy will be there to insure that the therapists at both sites will be administering therapies in the same way and will answer any question the therapists might have.

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:
* First Name: Burris
Middle Name: R.
* Last Name: Duncan
Suffix: M.D.

2. Human Subjects

Clinical Trial? ☐ No ☒ Yes

* Agency-Defined Phase III Clinical Trial? ☒ No ☐ Yes

3. Applicant Organization Contact

Person to be contacted on matters involving this application

Prefix:
* First Name: Sherry
Middle Name: L.
* Last Name: Esham
Suffix:

* Phone Number: 520-626-6000
Fax Number: 520-626-4137
Email: Sponsor@email.arizona.edu

* Title: Director

* Street1: P.O. Box 210158
Street2:
* City: Tucson
County/Parish:
* State: AZ: Arizona
Province:
* Country: USA: UNITED STATES
* Zip / Postal Code: 85721-0158

PHS 398 Cover Page Supplement

4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells? ☒ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/research/registry/. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): ☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Tracking Number:GRANT11413275 Funding Opportunity Number:PA-11-260 Received Date:2013-06-04T14:21:06-04:00

OMB Number: 0925-0001

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated for your reference, as you attach the appropriate sections of the Research Plan.

*Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. Introduction to Application (for RESUBMISSION or REVISION only)		Add Attachment	Delete Attachment	View Attachment
2. Specific Aims	1240-SpecificAims.pdf	Add Attachment	Delete Attachment	View Attachment
3. *Research Strategy	1241-ResearchStrategy.pdf	Add Attachment	Delete Attachment	View Attachment
4. Inclusion Enrollment Report		Add Attachment	Delete Attachment	View Attachment
5. Progress Report Publication List		Add Attachment	Delete Attachment	View Attachment

Human Subjects Sections

6. Protection of Human Subjects	1259-ProtectionOfHumanSubje	Add Attachment	Delete Attachment	View Attachment
7. Inclusion of Women and Minorities	1260-InclusionOfWomenAndMin	Add Attachment	Delete Attachment	View Attachment
8. Targeted/Planned Enrollment Table	1261-EnrollmentForm.pdf	Add Attachment	Delete Attachment	View Attachment
9. Inclusion of Children	1262-InclusionOfChildren.pd	Add Attachment	Delete Attachment	View Attachment

Other Research Plan Sections

10. Vertebrate Animals		Add Attachment	Delete Attachment	View Attachment
11. Select Agent Research		Add Attachment	Delete Attachment	View Attachment
12. Multiple PD/PI Leadership Plan	1263-MultipleLeadershipPlan	Add Attachment	Delete Attachment	View Attachment
13. Consortium/Contractual Arrangements	1264-ConsortiumAgreements.pd	Add Attachment	Delete Attachment	View Attachment
14. Letters of Support		Add Attachment	Delete Attachment	View Attachment
15. Resource Sharing Plan(s)		Add Attachment	Delete Attachment	View Attachment

16. Appendix Add Attachments | Remove Attachments | View Attachments

Specific Aims:

Cerebral palsy (CP) is a disorder of movement and posture caused by a non-progressive insult to the central nervous system when the brain is most rapidly developing. There is no known cure for CP but we hypothesize that an intense protocol of physical and occupational therapies can improve function in children with this condition. Current understanding of brain plasticity offers theoretical support for our hypothesis under the principle that active repetitive stimulation of non-injured but 'dormant' neurons prevents their 'natural' degeneration and promotes reorganization with the transfer of function from damaged neurons to intact ones. It is the very young brain that is most likely to respond to this intense therapeutic approach. Lower myelin content and elevated concentrations of trophic factors make the young brain more adaptable than an older one.[13, 23] This project will take advantage of the young brain's greater plasticity and is designed to stimulate this process of reorganization as early as possible. If we do not improve function early, the disability will continue into adulthood, often worsening and not only affecting the child's development but also have an adverse impact on the family and the community.

Studies have shown that repetitive activity stimulates neural growth and is represented by an enlarged area of the motor cortex corresponding to the anatomical set of muscles involved in the active movement.[13, 23] An intense series of therapies have been shown to be effective for functional recovery in animal models, rehabilitation interventions in adult stroke victims, and hemiplegic cerebral palsy.[13-16] Preliminary work performed by our group has shown that intensely administered physiotherapies significantly improved function of children between 12 and 72 months of age.[10] This work form the basis for our overarching proposal that will be pursued by the following specific aims: harnessing the capacity of the brain to reorganize (neural plasticity).

Specific Aim #1: To compare the effectiveness of an intense physiotherapy program with the current standard of care in the management of children with spastic cerebral palsy.

Hypothesis #1: Children receiving a short cluster of intense therapies (5 times a week for 12 weeks) will show greater functional gains as determined by the Gross Motor Function Measure (GMFM-66) and the Pediatric Evaluation Disability Inventory (PEDI) than those receiving the same therapies once a week, the current standard of care.

Specific Aim #2: To determine if the functional gains by children with spastic cerebral palsy achieved with an intense physiotherapy program will continue to improve while receiving less intense standard weekly therapies for at least 36 weeks (9 months) following completion of the intense program.

Hypothesis #2: Motor skills gained after 12 weeks of intensely administered physiotherapies as determined by the GMFM and the PEDI will continue to improve at a rate greater than that seen in children receiving the same therapies once a week, the current standard of care.

Specific Aim #3: After receiving the same number of therapies at the end of the 48-week protocol, children receiving the intense series of therapies during the first 12-weeks will have made greater functional gains than those receiving them during the last 12-weeks.

Hypothesis #3: Children who receive intense physiotherapies at an earlier age make greater gains then those who receive the same therapies at a later age.

Specific Aim #4: To develop a clinical profile that will identify those children most likely to benefit from intensely administered physiotherapies.

Hypothesis #4: Clinical and radiologic characteristics play a major role in response to therapy.

Explorative Aim: To assess the correlation between clinical improvement from intense physiotherapies and anatomical changes using magnetic resonance imaging (MRI).

Hypothesis: The improvements from intense physiotherapies seen in the clinical assessments will be reflected by alterations of brain connectivity parameters available from neuoranatomical MRI and diffusion tensor imaging (DTI).

5.5.3 Research strategy

(a) Significance:

The importance of the problem: Cerebral Palsy (CP) is a descriptive term for a group of disorders of movement and posture causing limitations or dysfunction of activity. The etiology is a non-progressive insult or injury to the central nervous system (CNS) when the brain is undergoing its most rapid development.[1] CP is the most frequent cause of childhood disability with overall prevalence rates in the U.S. of 3.1 per 1000 live births.[2]

It is estimated that approximately 70-80% of the insults to the CNS occur prenatally. Other etiologies include hypoxia during the perinatal period, postnatal CNS infections, exposure to toxic drugs, genetic abnormalities, and head injuries. The majority however, are the result of unknown or undetected mechanisms. Prematurity is the most frequent antecedent of CP, as it predisposes the infant to hypoxic-ischemic encephalopathy and intra-ventricular hemorrhage and often results in periventricular leukomalacia (PVL). Despite the intensiveness and multiple advances in neonatal care there has not been a significant decrease in the prevalence of CP. This is partially explained by the improved survival rate of the very low birth weight pre-term newborns.

Whereas the CNS insult is non-progressive, the effects from the motor deficit and muscle imbalance often worsen over time and may result in fixed contractures of major joints, progressive scoliosis, hip dislocation and body distortion. In addition, many affected children have other co–morbidities, such as varying degrees of intellectual disability, seizures, visual and hearing impairments, gastrointestinal problems, drooling, and recurrent aspirations. It is not surprising therefore that the estimated lifetime total healthcare cost per person with CP in the U.S. is $921,000.[3] Despite the frequency and high morbidity associated with this condition, there has been disproportional funding for research on CP.

There are essentially four different types of CP, each of which corresponds to an insult in a different area of the CNS. This study will concentrate on Spastic CP that accounts for ~75% of all individuals with CP. It occurs when the neurological insult involves the pyramidal area of the brain and is subdivided according to the number of limbs and which ones are involved i.e., monoplegic, diplegic, triplegic, quadriplegic, or hemiplegic. The severity of CP is based on the ability of the child to ambulate and is classified by the Gross Motor Function Classification System (GMFCS).[4] It varies from Level I (able to walk without assistance but with limited advanced gross motor skills) to Level V (severely limited mobility even with the use of assistive technology). Approximately 75% of children are classified as Level I, II or III. The degree of disability is closely related to survival. In 1995, the 30 year survival rate was 87%[5] and over the past 20 years, life expectancy has increased approximately 5 years.[6]

The current standard of care (SOC) for children with CP in the U.S. is physical therapy (PT) and/or occupational therapy (OT) usually administered formally once or twice a week and often directed at achieving goals set to improve motor function, improving strength and selective control, and maintaining range of motion. Medical management of spasticity may involve the use of orally administered muscle relaxants, injection of botulinum toxin, and continuous intrathecal infusion of muscle relaxants. Children with mild involvement often make progress, especially in early childhood, but those with more severe involvement show less improvement.[7] Surgical interventions such as tendon releases to alleviate contractures; de-rotational osteotomies and hip reconstructions to alleviate pain and/or improve sitting and standing balance; spinal fusion and rod placement for progressive scoliosis; fundoplication to prevent gastroesophageal reflux and gastrostomy tube placement to ensure sufficient fluid and nutritional intake may all be indicated for some children with CP. Conventional medicine is often unable to facilitate meaningful functional gains for many children with CP, especially if they are older or have more severe CP. Management in many eastern European countries and in China

is quite different. Physiotherapies are started earlier and administered 5 times a week for 12 weeks with improved clinical function.[8-10]

Critical barriers to progress:

- Despite new evidence of the ability of the young brain to adapt to insult, there is a persistent perception that children with cerebral palsy will "be like that forever".
- Few studies have evaluated the effectiveness of an intense approach using active-oriented physiotherapies in the management of CP. The few studies that have done so have had either a small sample size or have evaluated an older age population (when the brain is less adaptable), or have enrolled a diverse group of children with a broad range of severity of CP (the term cerebral palsy is too encompassing and each of the children with this 'diagnosis' or label is quite different and all children with CP will not respond to the same therapy).
- Parents do not have the time to take their child to therapies if given so frequently. Two Canadian investigators reported a 93% level of compliance with intermittent periods of therapies 4 times a week for 4 weeks followed by a rest of 8 week over a 6 month period.[11] We have just completed a study using the intense approach (5 times a week for 12 weeks) and found a 82% level of compliance. Using a qualitative approach on 5 children ages 4.9 to 8.8 years, Christy and others reported that despite the inconvenience of a program of 4 hours a day, 5 days a week for 3 weeks, the parents felt strongly that the gains were worth the effort.[12]
- There is a perception that our health care system cannot afford such an intense approach. If this approach will improve function with the consequence of decreasing spasticity, we cannot afford not to change the management of these children. The saving will be substantial in less need for medical devices and fewer surgical interventions for tendon releases alone. To decrease the cost of therapies, other approaches could be investigated such as training parents as co-therapists along with a concentrate on specific tasks to achieve particular skills.

Rational for physiotherapies started early and administered with intensity: The rationale for an intense series of active, repetitive, task-specific therapies administered to the very young child is based on observations in animal studies,[13] rehabilitation interventions in adult stroke survivors,[14] and a small number of investigations in children with hemiparetic cerebral palsy often secondary to "perinatal stroke".[15,16] Cortical reorganization is influenced by several factors: the precise location and size of the lesion; the age of the when the injury occurred; and the nature and extent of the rehabilitative training.[13]

Reorganization can be done in one of three ways: by recruitment of undamaged neurons adjacent to injured neurons; by recruitment of neurons from supplemental non-primary motor areas; or the stimulation of ipsilateral neurons.[13] If the lesion involves a small area, the immediate adjacent territory is reprogramed for lost function. If the lesion is larger and involves the adjacent territory, reprograming may recruit premotor cortical areas. Surgical lesions in newborn monkeys initially result in motor dysfunction but function gradually returns as areas adjacent to the damaged areas are reprogramed to assume the function of damaged neurons. If the lesion is very large, the intact opposite hemisphere may be recruited. The later situation is most dramatic in the young child who has undergone a hemispherectomy as radical treatment for uncontrolled seizures. Within days, the child is walking and shows only mild signs of hemiparesis. This is probably the result not only of intact ipsilateral connections but also of the removal of abnormal discharges from the contralateral dysfunctional hemisphere.[17]

The pathophysiology of an adult stroke is very similar to a perinatal stroke that has resulted in hemiparetic cerebral palsy. Even in the older brain, repetitive motor skill-directed rehabilitation promotes brain plasticity and can restore some function and is represented by an enlarged area

of the motor cortex. With no rehabilitation there is scant improvement in function and no increase in the cortical map representation. Constriction of movement of the unimpaired arm and hand of a stroke survivor for as little as 10 days improves function of the paretic arm and corresponding enlargement of the cortical representation of the affected upper extremity. In contrast, non-use of the paretic limb resulted in a decrease in the corresponding cortical representation.[18] Similar findings have been reported in children with hemiplegic CP with constraint therapy for just 6 hours a day for 10 days.[19]

The fact that a young brain is more adaptable with greatest neural plasticity potential than an older brain is due to several factors. There is less myelin in the young brain. Myelin has inhibitory influence on nerve regeneration. Tropic factors that stimulate nerve growth are in greatest abundance in the young. Ideally, this investigation should involve newborn infants as soon as neuroimaging detects lesions but for a number of reasons the diagnosis of cerebral palsy is delayed until 12 months and even beyond.

Cortical reorganization is based on the principles of motor learning which leads to sprouting of dendrites, formation of new synapses, alternation in existing synapses and production of neurochemicals.[20] The type of rehabilitative therapies that will induce neural reorganization has recently been reviewed by Arya and colleagues.[21] The changes are maximized and have long-term retention if the rehabilitation is repetitive, intense, and meaningful or skill-oriented. For example; the cortical map representation of the index finger of a Braille reader is larger than that represented by the adjacent fingers and is larger than on the ipsilateral cortex. A double armed amputee who has learned to use his right great toe to paint or sculpt shows an enlargement of the cortical area represented by the right great toe.[22]

Some basic principles are pertinent:[23]
1. There are critical times during neural development when a certain task is most easily learned.
2. Reorganization and reprograming of neural tissue is use-dependent (use it or lose it) and repetitive active movement has the greatest potential for stimulating neural growth.
3. A young brain is more adaptable than an older brain.

Evidence for an intense approach that is administered early: In 2010, Arpinoa and colleagues reported a meta-analysis on intense physiotherapies in children with cerebral palsy and found only 3 studies that satisfied their criteria of a randomized clinical trial, the word intense was in the title and was defined as greater than 3 times a week, and the Gross Motor Function Measure (GMFM) was used as the outcome measure.[24] They thus excluded studies that report positive results using other scales[25] such as the Pediatric Evaluation of Disability Inventory (PEDI) that provides information on daily life functioning. Bower et al evaluated 56 children all treated by a different therapist between 3 and 12 years of age and a GMFCS of level III or greater.[26, 27] These children showed a trend to improvement but it did not reach statistical significance. The RCT by Tsorlakis et al.involved 34 children between 3 and 14 years of age with mild to moderate CP (GMFCS I - III).[28] There was a statistical significant difference for the group that received the greatest effect of intense therapies (50 minute sessions 5 times a week for 16 weeks). Shamir and colleagues used a cross-over design to evaluate 10 patients 12-22 months of age and reported a gain of 7.8% in the GMFM for those receiving an intense approach as compared to a gain of 1.2% in those who received SOC.[29]

(b) Innovation:

A challenge to the current standard of care: The approach we propose challenges current practice in the Western world and it is supported by a clearer understanding of brain plasticity. It is now generally accepted that neurons in the central nervous system can be reorganized and reprogramed and intact neurons can assume the function of damaged neurons. Such changes are more easily done in the young brain. This proposal will take advantage of this physiologic window of opportunity. This will be the first large study involving very young children who will receive an intense series of physiotherapies and will correlate clinical changes with anatomical alterations using relative new technology, Diffusion Tension Imagining.

This proposal will evaluate an approach to a condition currently managed with less than optimal results in the U.S. If the approach is successful, we expect it to have impact at multiple levels:

- At the patient level: If children with this condition can improve their functional abilities through intensely administered therapies, their degree of independence will increase and as it does, improvement in other aspects of their lives (social, emotional and employment) will be seen.
- At the sub-set level: If we are able to identify historical, functional, or neuroimaging factors that predict response to intense early therapy, it would help direct optimal provision of services for maximum benefit and cost effectiveness.
- At the health policy and economy levels: A decrease in morbidity will lessen the tremendous burden of healthcare expenditure. Initiating intense therapies early has the potential of preventing at least some of the surgical procedures now being performed on children with CP.

An intense approach fits with current theoretical concepts of neuroplasticity: This proposal will take advantage of neuroplasticity of the very young brain shortly after a CNS injury with a program of intensely administered repetitive task-oriented physiotherapies. Although the standard of care for CP in some other countries includes an intense physiotherapeutic protocol, the specific type of therapy is not well described and there are very few studies that have assessed this approach with scientific vigor. It is not accepted practice in the United States. Our intent is to build on the study we recently completed in China[10] and if successful, to suggest that such an intervention be considered for children with spastic CP in this country.

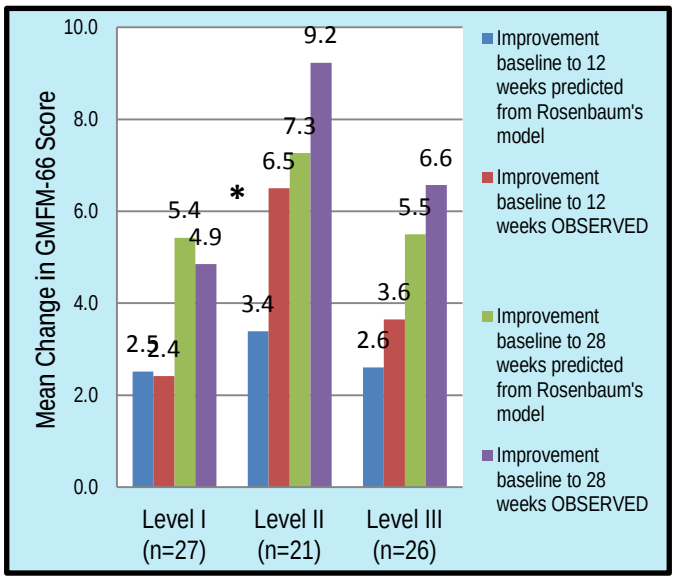
New methodologies to test theoretical concepts: An exploratory arm involving a small subset of children will determine if anatomical changes obtained from non-invasive neuroimaging correlate with clinical changes. If our hypothesis is correct, it will help to establish objective information that supports the long term outcome of intense early physiotherapy. Over the last few years, a number studies have demonstrated the value of diffusion tensor MRI (DTI) in the study of CP.[30-40] Measures of white matter integrity available through DTI, namely fractional anisotropy (FA) and mean diffusivity have been linked to motor dysfunction.[38-40] Changes in DTI parameters have also been correlated with treatment-induced improvement in CP.[31] MRI involves little risk and no long term side effects and it will be extremely helpful to include such studies in this project. It will allow us to determine if gains in function resulting from intensive-physiotherapy are reflected in neuroanatiomical changes observable with MRI. Such information will deepen our understanding of the mechanisms underlying therapeutic response and help further development of therapy. Additionally, if neuroanatomical features are discovered that predict the benefit that children gain from early intensive therapy, MRI could be used to preselect children for the appropriate type of therapy.

MRI/DTI is not the only tool to demonstrate cortical reorganization. Other tools include functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), and electromyography (EMG) for determining motor-evoked potentials. However, the children enrolled in our proposed study are too young to cooperate with the fMRI. An exact positioning of the skull cap used for TMS in two studies separated by 36 weeks in a rapidly growing brain and skull would be problematic. EMG is invasive and poorly tolerated by young children.

A shift in the current clinical practice of the same approach for all: From a clinical standpoint, this proposal will attempt to identify which children are most likely to respond to the intervention of early, intense, active, and repetitive therapy. CP is a condition with a wide degree of variation, a heterogeneous group of children and no one approach will fit all children. Some children in our China study (below) made very remarkable progress and others made little progress. The numbers did not allow the development of a profile but there was a suggestion that younger was better, that those with moderate severity improved more as did those with hemiparesis. If a profit emerges, it would be very helpful in predicting which children would improve and which had a lower potential for improvement.

(c) Approach

Preliminary investigations put us in a strong position to carry out this proposal: We recently completed a three-year, prospective, randomized controlled trial that took advantage of the SOC in China. In many children's hospitals in China, children with CP are hospitalized as soon as the diagnosis is made and receive four different therapies (PT, OT, hydro-therapy, and deep massage/acupuncture) 5 times a week for 12 weeks. Our study enrolled 115 children from which 75 had valid Gross Motor Function Measure-66 (GMFM-66) and the Pediatric Evaluation of Disability Inventory-Functional Skills (PEDI-FS) evaluations at baseline, 12 and 28 weeks. Massage/acupuncture did not appear to offer improvement but the intensity of the therapies did improve function. To determine the degree to which maturation might have influenced the results, the curves developed by Rosenbaum et al[7] were used to compare the changes in the GMFM-66 made by our children. Those with a GMFCS (Gross Motor Function Classification System) Level II made the greatest gains and at 12 weeks were significantly greater than the gains reported by Rosenbaum ($p < 0.01$). The gains by those with a GMFCS Level III were considerably greater than the gains reported by Rosenbaum but did not reach statistical significance. PEDI results mirrored the GMFM findings with higher scores at the end of 12 weeks and some continued improvements were seen at the 28 week evaluation.[10]



Using the levels of responsiveness analyses based on a change in GMGM-66 Wang and Yang[41] reported on the basis of clinical improvement, our children with a GMFCS Level II would have been classification as "greatly improved". The mean age of the children they assessed was greater than the children in our study and the changes they reported were considerably less than what we found: Level I, 1.7 and 2.7; Level II, 1.0 and 1.5, Level III, 0.7 and 1.2 respectively for a medium and large change of clinical importance.[42]

We realized that what can be done in China may not be feasible in the U.S. Therefore we conducted a small feasibility study in Tucson, AZ to determine if parents of a child with cerebral palsy could/would comply with the same intense protocol of administering PT and OT on an outpatient basis 5 times a week for 12 weeks. Sixteen children between the ages of 18 and 36 mos. completed the study with a compliance rate of 82%. Parent satisfaction was universally very high. Even with a very small sample size, when compared with Rosenbaum's curves,[7]

GMFM-66 scores met statistical significance for children with a CMFCS Level I ($p = 0.51$) as did the combined average of scores for all children in Level I, II, and III. ($p < 0.048$).

A qualitative study on this same population involved four-hour extensive interviews with 8 of the mothers (the others could not be contacted). Seven of the 8 were positive about the gains in function their child achieved and found the intense therapy schedule was feasible. Six of the eight said they would do it again and the other two mothers would if the clinic was closer to home. All 8 reported significant improvement in their child's motor functioning, strength, flexibility, socialization, independence, and sensory issues. Moreover, parents left the study "feeling informed," with a new repertoire of tools to use with their children at home. One parent reflected on the lasting effects of the intensive study; "After 12 weeks of intense stretching and strength training, he continues to use his right hand, it opens a whole new world for him. He can climb onto his rocking chair by himself, carry things by himself. We crossed a bridge that allowed him to improve more because he could do more things."

The proposed study is a bi-center randomized clinical tri**al** in a block design, stratifying by age (12 through 24 months and 25 through 36 months of age) and disease severity level (GMFCS Levels I, II, and III). It will enroll 110 children; 80 at the Phoenix Children's Hospital (PCH) and 30 at the Outpatient Therapy unit at the Tucson Medical Center (TMC).

Inclusion criteria:

1. *Age:* 12 to 36 months of age (The diagnosis of CP is often uncertain under the age of 12 months. The cutoff of 36 months is to have a population of young children when the brain is most 'plastic' and most susceptible to reorganization).
2. *Diagnosis:* Diagnosis of spastic CP confirmed by a pediatric neurologist or pediatric rehabilitation specialist.
3. *Etiology:* The insult to the CNS that caused the motor dysfunction must have occurred during gestation or within one month after birth independent of gestational age.
4. *Disease severity level*: GMFCS levels I, II, and III

Exclusion criteria:

1. *Diagnosis:* Diagnosis of CP secondary to neuronal migration.
2. *Co-morbidities*: Medical conditions that may prevent the administration of rehabilitation therapies at the intensity required by the study, or that may compromise the study ability to maintain blindness, or that have a co-morbidity not typically associated with CP (i.e. cancer, cystic fibrosis).
3. *Co-interventions:* Anticipated pharmacological intervention or procedure or participation in other studies that may interfere with this study.

Level of motor involvement (CP severity) will be assessed by the Gross Motor Function Classification System (GMFCS).[43] Walking is used as the qualifier, but for children who are too young to walk other activities are used. The 5 Levels of severity are based on GMFM scores with Level 1 the less severe.

Upon randomization, each child in both arms of the study will be expected to complete a 48 week protocol. Group 1 will receive 30 minutes of PT and 30 minutes of OT each weekday for 12 weeks and then these two therapies will be given once per week for the next 36 weeks (SOC). Group 2 will receive the same therapies once per week for 36 weeks (SOC) and then receive the intense protocol for 12 weeks. By the end of the 48-week protocol, both Groups will have been scheduled to receive 96 sessions of PT and 96 sessions of OT and 5 sets of evaluations.

The rehabilitative therapies: The type of therapy to be administered at both centers is Perception Action (P-A). The Rehabilitation Children's unit at TMC has been administering this therapeutic approach for more than 8 years.[44-49] Mary Lou Fragomeni, Chief of therapies at

TMC and Dr. Brandys, Co-Investigator, Pediatric Physiatrist and Chief of Pediatric Rehabilitation at the PCH will insure that the PA therapy is in accordance at both centers. The P-A (motor) intervention approach utilizes current principles of neuroplasticity and adaptability of movement. It is built on the premise that movement is influenced and assisted by information gained from the environment. The ability to act or move is a product of the constraints of the individual (flexibility, strength, motivation) and of the environment (texture or slope of the surface, external touch and support, distractions, and presence of objects the child is seeking). P-A is a child-driven approach without the need for special equipment and considers the child and the environment as a single unit. Even a small change in the environment produces a significant reaction or movement in the child. Perception of the environment and the child's reaction to it are one; a dynamic interacting unit.

Treatment is a coupling of the child with the environment. The environment is changed to enable, enhance or stimulate movement. The action is initiated by the child with the therapist augmenting the child's environment using touch (tactile information) or light support (cushions, bolsters, and gentle touch or pressure) to assist and/or alter the child's active movement. The therapist guides the action but does not direct or perform the movement for the child. As the support changes, the child will change their motor strategies to achieve their goal. This approach is most relevant and appropriate to the infant or toddler whose movements are not predictable and who either cannot or has difficult following verbal instructions; a situation most pronounced in the child with CP. The therapists adapts to the child's schedule, interest, and initial movement. Toys are used and positioned in different places to encourage movement of upper and lower extremities and the trunk; reaching, turning, sitting balance, crawling, walking. The key is active (not passive) movement. The P-A framework is in concert with the understanding of brain plasticity.

Evaluations, endpoints, and timing: The primary aim is to assess function. The evaluation instruments we chose are standard in CP research and include an assessment by a certified therapist of gross motor function (GMFM-66) and a parental assessment of the child's functional abilities in the home environment (PEDI-FS). For the primary and secondary outcomes, these endpoints will be assessed at baseline and at 12 weeks (**SA #1**) and every 12 weeks for the next 36 weeks (**SA #2 and #3**). (Table) The evaluation at 48 weeks after the completion of the intense schedule allows an estimation of the persistence of change (**SA #3**).

The GMFM-66[50-52] is a criterion referenced validated instrument that has been shown to detect change in gross motor function (performance) of children with CP as a result of various interventions, [27, 53-55] Using multiple longitudinal observations with the GMFM, Rosenbaum et al. have developed motor development curves for children with different severity levels that can serve as a basis for prognosis and therapeutic progress.[7] The 66 test items have been grouped into five dimensions: Lying and rolling, Crawling and kneeling; Sitting, Standing, and Walking, running and jumping. Scores will be obtained using the computerized software program that calculates the total score: the Gross Motor Ability Estimator (GMAE). For the scoring therapists, a training video will be used that has been shown to improve the reliability of therapists scoring from a video from a mean kappa of .81 to a mean of .92.[10, 56]

The PEDI-FS is an instrument developed specifically for children from 6 months through 7 years of age who some type of a disability.[56-57] It is child's primary care provider's assessment of what skills the child is able to perform. The skills are grouped into 3 domains: (1) self-care, (2) mobility, and (3) social function. The raw scores from each of the 3 domains are transformed into scaled scores and total scores. We have shown satisfactory reliability between parents and therapists and responsiveness to change.[58]

Specific Aim #1 *Does an intense series of therapies improve function to a greater extent than the current standard of care for children with spastic cerebral palsy?*
Specific Aim #2 *Is the improvement* that was obtained after the intense series (Group 1) maintained for at least 36 weeks (9 months)?
Specific Aim #3 *If therapies are administered at an earlier age, is the improvement greater than if it is administered at a later age?*

Primary outcome (Specific Aims 1, 2, 3): A difference in the GMFM-66 scores between those children in Group 1 and those in Group 2 as outlined in the first 3 Specific Aims.
Secondary outcomes (Specific Aims 1, 2, 3): A difference in the PEDI-FS scores between those children in Group 1 and those in Group 2 as outlined in the first 3 Specific Aims.

Groups	0 to 12 weeks	13 to 24 wks.	25 to 36 wks.	37 to 48 wks.	Total therapies
Group 1 Early intensive therapies N = 50	Intense therapy 5 times a week for 12 weeks 30 min. sessions 60 of PT and 60 of OT	Standard Rx Once a week 12 therapies of PT and of OT	Standard Rx Once a week 12 therapies of PT and of OT **Specific Aim #2**	Standard Rx Once a week 12 therapies of PT and of OT	PT = 96 OT = 96
Group 2 Later intensive therapies N = 50	Standard Rx Once a week 12 therapies of PT and of OT	Standard Rx Once a week 12 therapies of PT and of OT	Standard Rx Once a week 12 therapies of PT and of OT	Intense therapy 5 times a week for 12 weeks 30 min. sessions 60 of PT and 60 of OT	PT = 96 OT = 96
Evaluations GMFM-66 PEDI-FS	Baseline and at 12 weeks **Specific Aim #1**	24 weeks	36 weeks	48 weeks **Specific Aim #3**	Total = 5

Rationale and Methodology for SA 1, 2, & 3: SA 1 will compare recovery after 12 weeks of intense physiotherapy with the current standard of care in very young children. **SA 2** will assess if the gains are maintained during the time when the frequency of the therapies reverts to the current SOC. **SA 3** will determine if the window of opportunity for recovery is wider at an earlier age. The trajectory of the gain for children receiving the intense protocol early (Group 1) will be compared with the trajectory of gain attained with the ones (Group 2) from those receiving the current SOC. The two age groups (12-24 mos. and 25-36 mos.) will be compared to look at the window of opportunity.

Specific Aim #4: *To develop a clinical profile for children that will most likely benefit from intensely administered physiotherapies.*

Rationale and Methodology for SA #4: Previous efforts from our group as well as other investigators have shown that some children responded very well to the intervention, while others had only a very small response. Cerebral palsy is not a specific term and it does not define the etiology, timing, location or severity of the CNS insult. Children who have this diagnosis are a heterogeneous group. The purpose of this aim is to develop a “clinical profile” that will help predict the response to intense physiotherapeutic intervention. Regression analysis will be used to develop a clinical profile from data obtained from the clinical history, the physical examination, and MRI findings to help predict the likely response to this approach.

Rationale and outline for the blind evaluation methods: Our evaluation plan was designed to maximize objective outcome assessment while minimizing performance bias. To eliminate ‘stranger anxiety’ with the introduction of an ‘evaluation therapist’, administration of the GMFM-

66 will be done by the child's treating therapist but the scoring of the test will be done by a different certified therapist. Videos are used in training therapists to score the GMFM.[59] The proposed observation systems at each site include a mobile observation/recording system consisting of two high-quality cameras and a laptop computer with dedicated proprietary observation and capture software. The system, produced by B-Line Medical (an industry leader simulation recording, observation and reviewing hardware and software), will capture the therapist's interactions and the child's response at each site from two camera angles insuring that every movement of the child is recorded. The simultaneous recordings are automatically synced and the combined video stream packaged and delivered to the B-Line server software housed at the data center at the University of Arizona, College of Medicine (U of A COM).

The certified reviewers will be 'blinded' to the child's group assignment and the 5 sets of evaluations will be shuffled so the scorer will also be 'blinded' to the sequence of the evaluations. The reviewer will be able to view playback of the sessions from any web-based computer and evaluate the performance of the subjects. Evaluators will be able to either view both cameras simultaneously or switch to larger views of either video recording. (Appendix).

Data management and coordination (including handling of missing data and outliers): All data and video recordings will be stored on a password-protected web site designated for-and dedicated to-this study by John Hall, Director of the Division of BioCommunications and his staff at the U of A COM. Written standard operating procedures will be used to protect data from error, negligence, misconduct, conflict of interest, malicious acts, and catastrophe. Data from each session will be entered on standard paper forms (Appendix) and then entered into the dedicated computer database within 48 hours of collection by the Project Coordinators at each site. The data will be checked for incorrect and missing values, evaluated for outliers, and then edited. A 10% check against original records will be made to ensure less than a 1% error rate. Computer files will be simultaneously backed up on the College of Public Health server. Efforts will be made to minimize attrition and correct other sources of missing data. To further minimize the amount of missing data we will use only focused standardized instruments that are familiar to the researchers and avoid overburdening subjects with data collection. Safety data will be documented and adverse events will be promptly investigated throughout the study period.

Explorative Aim: *To determine the correlation between clinical improvement from intense physiotherapies and anatomical changes using magnetic resonance imaging (MRI).*

Rationale for the Exploratory Aim: There is strong evidence that non-invasive imaging measures available via MRI demonstrate neuroanatomical deficits that are correlated with motor and cognitive deficits in CP. In a recent literature review of studies of white matter integrity and structural connectivity in children with CP, Scheck et al. conclude that diffusion-based MRI, specifically, has provided new insight in to the specific injury and reorganization of white matter motor pathways and improved understanding of the structure-function relationships between corticomotor and sensorimotor networks.[60] Recently, whole brain connectivity analysis of DTI data has shown diffuse white matter abnormalities throughout the brain and specific reduction in long-range connections in severe CP.[39] Such studies have been included into therapeutics trials.[31, 39] Inclusion of MRI into the proposed project will allow objective assessment of neuroanatomical changes associated with clinically observed neuroplasticity in early interventions.

Methodology and analyses for the Explorative Aim: Imaging studies will be done at the Barrow Neurological Institute of the PCH on a small, homogeneous subset of children that have a history of prematurity with periventricular leukomalcia. Ten children from each of the two randomized groups stratified for age and severity will be imaged before therapy and at 36

weeks after the beginning of therapy. Group 1 will have received 12 weeks of intense physiotherapies followed by the SOC and Group 2 will have only received the SOC. Each MRI examination will include the following sequences: 1) A scout image for planning purposes; 2) A 3D T1-weighted inversion-recovery-prepped 3D (MPRAGE) sequence will be used to generate neuroanatomical images which will be used for evaluating regional distributions of gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). This sequence has been used in previous studies of development and has proved useful for differentiating regional development of brain tissue in children with CP.[39, 61] Diffusion Tensor Imaging (DTI) will be used to evaluate the functional organization and integrity of WM. A diffusion-weighted single-shot spin-echo echo-planar imaging sequence (parallel acceleration = 2) will be implemented that will measure brain water diffusion along 30 non-colinear directions. 5 minimally diffusion-weighted images (b = 0.03 ms/μm^2) will be collected along with 30 diffusion-weighted (b = 1 ms/μm^2) images; 4) 2D T2-weighted fast spin echo images, co-localized to the DTI data, will be acquired and will be incorporated into the DTI processing pipeline to correct for residual distortions due to magnetic field inhomogeneity. The MRI examination including all images will be <30 minutes.

Processing and analysis of MRI data will be done by Dr. Theodore Trouard, Co-Investigator and Associate Professor of Biomedical Engineering and of Medical Imaging and Assistant Director of the BIO5 Institute (U of A). The purpose of this subset is to evaluate white matter integrity and connectivity throughout the entire brain. It is important to note that the image acquisition will allow multiple ways to evaluate connectivity in the brain. Two different methods that will be used are tract-based spatial statistics[62] and an atlas-based connectivity methodology. DTI data will be initially processed using FSL software[62] including correction for motion and eddy-currents. Image distortion from B0 inhomogeneity will be corrected using non-linear warping to the T2-weighted FSE images acquired coplanar with DTI via large deformation diffeomorphic metric mapping (LDDMM). Fractional anisotropy (FA) and mean diffusivity (MD) maps will be computed using standard algorithms.[63.] TBSS will be applied to evaluate differences in white matter tracts between experimental groups. FA maps from each group will be registered to a common template generated from the entire cohort. We expect that no significant differences will be seen in the groups prior to therapy. Differences at 36 weeks will be indicative of alterations in white matter due to therapy. Atlas-based connectivity measures will also be determined in a way similar to that recently described[39] that utilizes a previously generated atlas[64] to allow automatic identification of regions of interest in the gray matter and evaluate interregional connectivity between them. Connectivity scores will be compared between groups and across time in individual children. Our hypothesis predicts that increases in connectivity will be observed following intense therapy and that at 36 weeks, individuals in Group 1 will exhibit greater increases in connectivity measures than those in Group 2. Because of the young age of the children in the study, increases in brain connectivity is expected due to normal development over 36 weeks in both groups of children. To account for this, groups will be counterbalanced in age and disease severity and time will be used as covariate.

Enrollment procedure: Children will be recruited from the greater from the greater Phoenix area (80) and from the Tucson area (30). At both sites, informing parents of the study will be done by medical staff at the Children's Rehabilitative Services Clinic, by pediatricians, pediatric neurologists, and case workers and therapists working with the Division of Developmental Disabilities. If a parent seems interested in enrolling her/his child in the study, he/she will be given contact information of the specific site Study Coordinator. The study will be briefly explained over the phone and if interest continues, a face-to-face private meeting will be arranged when a more in-depth explanation will be given. The consent form will be explained, and questions will be answered. Special efforts will be made to assure that the parents understand what randomization means and what co-interventions are allowed or not allowed. Only then, will they be asked to sign an informed consent. After signing, the Study Coordinator

will enter into a password protected web-based study database a scanned copy of the signed informed consent, the participant information including age and GMFCS severity level and an appointment for the first evaluation and beginning of treatment. That information will be checked by Dr.Chengcheng Hu, Biostatistician to ensure that the enrollment process was impeccable. Only then, will randomization take place.

Subjects' retention: To help keep attrition under 10%, all study treatment associated costs not covered by insurance will be covered by the grant; close contact with families will be maintained through biweekly phone calls and will be used to monitor and document any protocol deviations note progress or regression as assessed by the parents (Appendix), learn about any planned moves or other changes in home life and remind parents of the scheduled treatments; and mail personal thank you letters to the parents every 12 weeks following each evaluation.

Sample size and power for the RCT: Each of the primary and secondary outcome measures will be compared between the two randomized groups by the Wilcoxon rank-sum test. In our feasibility study conducted in Tucson, AZ, 10 children of GMFCS levels I through III showed a mean improvement in GMFM-66 score of 6.02 over 12 weeks with standard deviation (SD) of 4.28. For the power analysis we assume a similar distribution in the primary outcome of 12-week change of GMFM-66 score for Group 1. For the 10 children in the feasibility study the expected changes in GMFM-66 score over 12 weeks without intensive therapies were also calculated according to the Rosenbaum model and the mean is 3.38. This is assumed to be the mean change in the primary outcome measure for Group 2, and SD in this group is assumed to be the same as that of Group 1. For the sample size of 50 children per group, out study will have a power of 84% to detect the difference in the primary outcome measure. With a 10% loss-to-follow-up rate the power will be 80%. According to the rationale above for Specific Aims 1, 2 and 3, we expect that the GMFM-66 score for subjects in Group 1, with intensive therapy given early, will keep improving after 12 weeks at a faster rate than that of children in Group 2, even after Group 2 receive intensive therapy at a later stage. Thus the power analysis given above also applies when comparing secondary outcome measures of 36-week and 48-week changes in GMFM-66 scores. For the secondary outcome measures of change in each of the three PEDI scores (self-care, mobility, and social function), data on 12-week change were available from six subjects in the Tucson feasibility study. Assuming that for each PEDI score the mean change in Group 1 is the same as that in the feasibility study, the mean change in Group 2 is half as much as that in the feasibility study, and the SD for both groups is the same as that in the feasibility study, the power for comparing the PEDI scores ranges from 82% to 99% when the loss-to-follow-up rate is 10%.

Statistical Analysis: Analysis will be performed using SAS and R by Dr. Chengcheng Hu, Biostatistician and Associate Professor of Public Health at the U of A. Baseline characteristics (such as age, gender, severity level and GMFM-66 and PEDI scores) will be summarized for each group. The randomization will be evaluated by comparing distributions of these characteristics between groups using Fisher's exact test and Wilcoxon rank-sum tests, as appropriate. Wilcoxon rank-sum tests will be used to compare each of the primary and secondary outcome measures between the two groups (Specific Aims 1, 2, and 3). The test will be two-sided with significance level 0.05. The analysis will follow the intent-to-treat (ITT) principle and impute any missing data using the last-measurement-carry-forward method. For Specific Aim 4 the trajectories of GMFM-66 and PEDI scores over 48 weeks will be predicted by intervention pattern, compliance to treatment, age at randomization, gender, and baseline scores using generalized estimating equation (GEE) models. Analysis for the exploratory aim will be descriptive, with summary statistics calculated for each group.

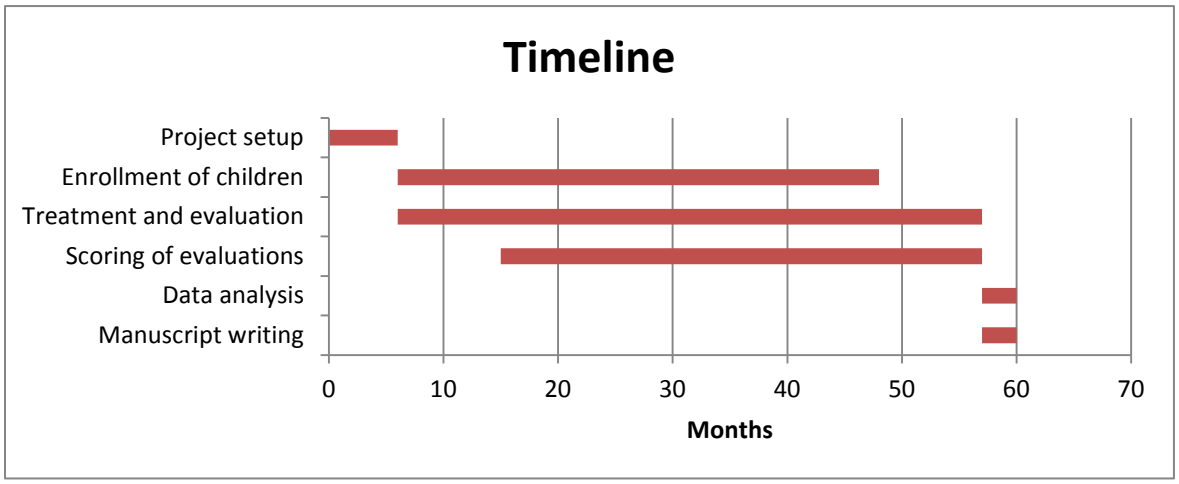
Assessment of the integrity and fidelity of the study interventions: Each therapist will keep treatment logs describing the type of activity and duration of the treatment received at each treatment session (Appendix). The logs will also have information relative to the amount of 'therapy' the parents were doing with the child between formal therapy sessions. Every 12 weeks, parents will be asked to complete a questionnaire documenting the amount of time they spend with their child in home 'therapy'. Bi-weekly phone calls made by the study coordinator and described above will encourage compliance with the protocol.

Study limitations and potential threats to validity:

Co-interventions: We will monitor all co-interventions with every other week phone calls and consider them in our final analyses as covariates (Appendix).

Maturation: At this young age, a child's brain is in a rapid stage of development complicating the outcome analysis. That is the reason we have stratified enrollment by age and if randomization is successful, there should be equal distribution of age groups in both arms of the study.

Study timeline: The first six months will be used to put the investigation in place and begin the campaign to alter child care providers of the study. All who are involved in the study from both sites will have orientation sessions to insure coordination and cohesion between the two sites. Enrollment will continue for 42 months with therapies and evaluations that will be completed by 57 months allowing 3 months for analysis of the data and writing of manuscripts. Time will be allotted to explore other research projects stimulated by our study, and if our hypotheses are confirmed, to begin the process of planning a Phase III confirmatory clinical trial.



4.1 Protection of Human Subjects

"This Human Subjects Research meets the definition of a clinical trial."

4.1.1 Risks to Human Subjects

a. ***Human Subjects Involvement, Characteristics, and Design***

• Proposed involvement of human subjects

This study is being done to determine if a more intense series of physical and occupational therapies is more effective in helping young children with cerebral palsy improve their motor function than is the current standard of care.

• Characteristics of the subject population

We expect to enroll 110 children between the ages of 12 and 36 months who have been diagnosed with cerebral palsy in this study. Approximately 80 of the children will be enrolled from the Phoenix area and 30 from the Tucson area.

• Sampling plan, recruitment and retention strategies, and inclusion and exclusion criteria

Children will be recruited from the greater Tucson area and from the greater Phoenix area. Informing parents of the study will be done by medical staff at the Children's Rehabilitative Services Clinic, by pediatricians, pediatric neurologists, and case workers and therapists working with the Division of Developmental Disabilities.

The following methods will be used to keep attrition at less than 10%:

- All study associated treatment costs not covered by insurance will be covered by the grant.
- Every other week phone calls with the families to:
  - Monitor and document any protocol deviations (auxiliary treatments),
  - Note progress or regression as assessed by the parents,
  - Learn about any planned moves or other changes in home life,
  - Remind parents of the scheduled treatments, and
  - Personal thank you letters to the parents every 12 weeks following each evaluation

Inclusion criteria:

1. Age: Children between the ages 12 and 36 months. The diagnosis of CP is often uncertain under the age of 12 months. The cutoff of 36 months is to have a homogeneous population of young children when the brain is most 'plastic' and most susceptible to reorganization.
2. Etiology: The insult to the CNS that caused CP must have occurred during gestation or within one month after birth and may be associated with prematurity.
3. Diagnosis: The diagnosis of spastic CP must be confirmed independently by a pediatric neurologist or pediatric rehabilitation specialist
4. CP severity level: Gross Motor Function Measure Classification System (GMFCS) levels I, II, and III

Exclusion criteria:

1. Cerebral palsy secondary to neuronal migration.
2. Co-morbidities: Co-morbidities that are contraindication for rehabilitation therapies that may compromise our ability to maintain blind evaluations, and that are of a serious nature not typically associated with CP (i.e. cancer, cystic fibrosis).
3. Co-interventions: Children whose parents/caregivers will not consent to not altering the dose of any anti-spasticity medications their child may be on and will not consent to not providing their child with any formal CP-related therapy during the 48 week
4. Co-participation in another CP trial that potentially might conflict with this trial.

Children between the ages of 12 and 36 months will be randomized but stratified by age (12 through 24 or 25 through 36 months) and severity (GMFCS I, II, or III) into Group 1 (early intensive therapies) or Group 2 (later intensive therapies). Group 1 will receive 30 minutes of PT and 30 minutes of OT each weekday for 12 weeks and then these two therapies will be given once per week for the next 36 weeks. Group 2 will receive the same two therapies once per week for 36 weeks and then receive the intense protocol for 12 weeks. By the end of the 48-week protocol, both Groups will have been scheduled to receive 96 sessions of PT and 96 sessions of OT. Evaluations will be done at baseline and every 12 weeks thereafter, a total of 5 sets of evaluations. Evaluations will use two different instruments, the Gross Motor Function Measure-66 (GMFM-66) and the Pediatric Evaluation of Disability Inventory-Functional Skills (PEDI-FS).

• Rationale for the involvement of children

Cerebral palsy (CP) is the most frequent cause of childhood disability with overall prevalence rates in the U.S. of 3.1 per 1000 live births. Cerebral Palsy is a descriptive term for a group of disorders of movement and posture causing limitations or dysfunction of activity caused by a non-progressive insult or injury to the central nervous system when the brain is undergoing its most rapid development. Despite the intensiveness and multiple advances in neonatal care there has not been a significant decrease in the prevalence of CP. This is partially explained by the improved survival rate of the very low birth weight and very pre-term newborn infant. Other etiologies of CP include hypoxia during delivery, postnatal CNS infections, and head injuries.

The current standard of care for children with CP in the U.S. is physical therapy (PT) and/or occupational therapy (OT) usually administered formally once or twice a week and often directed at achieving goals set to improve motor function, improving strength and selective control, and maintaining range of motion. Medical management of spasticity may involve the use of orally administered muscle relaxants, injection of botulinum toxin, and continuous intrathecal infusion of muscle relaxants. Children with mild involvement often make progress, especially in early childhood, but those with more severe involvement show less improvement. Surgical interventions such as tendon releases to alleviate contractures; de-rotational osteotomies and hip reconstructions to alleviate pain and/or improve sitting and standing balance; spinal fusion and rod placement for progressive scoliosis; fundoplication to prevent gastroesophageal reflux and gastrostomy tube placement to ensure sufficient fluid and nutritional intake may all be indicated for some children with CP. Conventional medicine is often unable to facilitate meaningful functional gains for many children with CP, especially if they are older or have more severe CP.

The standard of care in many eastern European countries and in China is quite different. Physiotherapies are started earlier and are administered five times a week and usually continued for 12 weeks. Numerous investigations report improved functional outcomes and a decreased need for invasive procedures.

• Procedures for assignment to a study group and intervention

Once the child is enrolled in this study, he/she will be randomized into one of two groups. Group 1 will receive an intense series of physical and occupational therapies (each weekday 5 times a week for a total of 12 weeks) and then for the following 36 weeks the frequently of these two therapies will decrease to once per week (the current standard of care for children with cerebral palsy). Group 2 will receive these two therapies once a week for the first 36 weeks and then will receive the intense series for the following 12 weeks. at the frequency that is the standard of care, once each week and then will receive the intense series for the next 12 weeks. Each of

the therapy sessions will be 30 minutes in length with a 15 minute break between the two therapies. Every attempt will be made so the two therapeutic sessions will be administered back to back with the 15 minutes of rest in-between. This study will last for 48 weeks.

• Collaborating sites

The therapies and the administration of the evaluations will be done at one of two sites. Children living in the Phoenix metropolitan area will be seen in the Rehabilitation Unit at Phoenix Children's Hospital in Phoenix, Arizona. Children living in the Tucson metropolitan area will be seen at the Outpatient Pediatric Therapies Center at the Tucson Medical Center in Tucson, Arizona.

Subset of the larger investigation

• Proposed involvement of human subjects

A small sample of a larger enrollment of children will be recruited to determine if there are any changes in the nervous structure of the child's brain that correlate with the changes in function seen in the child.

• Characteristics of the subject population

We expect to enroll 20 children between the ages of 12 and 36 months in this portion of the study. It is anticipated that all the children will live in the greater Phoenix area. Half (10) of the children will have been enrolled in Group 1 and half (10) in Group 2.

Inclusion criteria:

1. A participant in the larger study
2. A premature birth
3. Damage to neurons above the ventricles of the brain, periventricular leukomalcia (PVL)

Procedures for assignment to a study group and intervention

The children in this portion of the study will have two MRI/DTI studies, one at baseline and the other at 36 weeks following their respective therapies. The children will be lightly anesthetized during the procedure (30-45 minutes) and closely monitored by a certified anesthesiologist until fully awake.

Collaborating sites

All of the imagining studies will be done in the Department of Radiology - Clinical MRI Department at the Barrows's Neurological Institute at the Phoenix Children's Hospital.

b. ***Sources of Materials***

• Material obtained from living individuals

None

• Data that will be collected

Two different outcome measurements will be done in this study.

1. The initial evaluation will include taking the child's medical history, assessing the strengths and weakness of the child's abilities, determining the severity of motor involvement as assessed by the Gross Motor Function Classification System, and setting task-specific goals.

2. The primary outcome measure is change in Gross Motor Function that will be assessed by the GMFM-66; a criterion referenced validated instrument. It will be administered by the child's treating physical therapist. The evaluation will be recorded and stored on a password-protected web site and later scored by another certified therapist who is 'blinded' to which group the child was assigned. This evaluation will be done 5 times during the 48-week protocol.
3. A secondary outcome measure is the Pediatric Evaluation Disability Inventory. This is an instrument developed to assess the functional abilities of children from 6 months through 7 years of age designed specifically for children with chronically illness. It is a questionnaire that will be completed by the child's principal care-giver. This evaluation will be done 5 times during the 48-week protocol.

Each treating therapist will keep treatment logs describing the type of activity and duration of the treatment received at each treatment session. The logs will also have information relative to the amount of 'therapy' the parents were doing with the child between formal therapy sessions. Every 12 weeks, parents will be asked to complete a questionnaire documenting the amount of time they spend with their child in home 'therapy'. Bi-weekly phone calls made by the study coordinator and described above will encourage compliance with the protocol.

Subset of the larger investigation

• Data that will be collected

Each child in this portion of the study will have two special MRI examinations, Diffusion Tension Imagining or DTI. One will be done prior to starting the therapies and the other will be done at the end of 36 weeks. This study is done using the same machine and the same technique as is done with a regular MRI. And as with the regular MRI, no substances will be injected into the child. The only difference is in how the images are analyzed. The DTI allows the radiologist to see how nerve fibers are connected with each other. This small subset of the larger study is being done to see if the intense therapies produce greater nerve connectivity than does the standard frequency of therapies for children with cerebral palsy.

• Access to individually identifiable private information about human subjects

Efforts will be made to keep study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies
- The University of Arizona Institutional Review Board or Office of Responsible Research Practices
- The National Institutes of Health, the sponsor that is supporting the study, their agents or study monitors

• How data are collected, managed, and protected

Data from this study will be collected by one of two Project Coordinators who will transfer the data onto a password protected web site. Scoring therapists will have access to the tapped recorded gross motor function examinations. The Bioengineer and the Graduate Student

working with him will have access to the MRI/DTI images of the 20 children in the subset. The Principal Investigators and Key Personnel will have access to the data.

c. ***Potential Risks***

• Potential risks

The therapies that administered to your child are no different than the therapies that are usually recommended for a child with cerebral palsy. The only difference is the frequency that the therapies will be given.

• Alternative treatments and procedures

None that would be of less risk

Subset of the larger investigation

• Potential risks

Since it is necessary that the patient having an MRI be very still during the procedure and this can be very difficult for young children, the child will be given a light anesthesia. This will be done by an anesthesiologist who will very carefully monitor the child during the procedure and will continue the monitoring until the child is sufficiently awake. The entire procedure should not take more than 30-45 minutes.

4.1.2 Adequacy of Protection Against Risks

a. ***Recruitment and Informed Consent***

• Plans for the recruitment and process for obtaining informed consent

Children will be recruited from the greater Tucson area (approximately 30) and from the greater Phoenix area (approximately 80). Informing parents of the study will be done by medical staff at the Children's Rehabilitative Services Clinic, by pediatricians, pediatric neurologists, and case workers and therapists working with the Division of Developmental Disabilities. If a parent seems interested in enrolling her/his child in the study, he/she will be given contact information of the study coordinator. The study will be briefly explained over the phone and if interest continues, a face-to-face private meeting will be arranged when a more in-depth explanation will be given. The consent form will be explained, and questions will be answered. Special efforts will be made to assure that the parents understand what randomization means and what co-interventions are allowed or not allowed. Only then, will they be asked to sign an informed consent. After signing, the Study Coordinator will enter into a password protected web-based study database a scanned copy of the signed informed consent, the participant information including age and GMFCS severity level and a target date for the first evaluation and beginning of treatment. That information will be checked by Dr. Hu to ensure that the enrollment process was impeccable. Only then, will randomization take place.

b. ***Protections Against Risk***

• Procedures for protecting against or minimizing potential risks

Risks of injury from participating in this study are minimal. The facilities where the therapies will be administered have been doing these same therapies for a very long time and are well equipped to care for any unforeseen injury or problem that may occur. If you suffer an injury from participating in this study at a time when you are not in the facility, you should seek

treatment. The University of Arizona has no funds set aside for the payment of treatment expenses for this study.

• Additional Protections for Children

The therapies to be administered in this study are no different than those that are recommended as the standard of care for children with cerebral palsy, it is only the intensity of the therapies that is different and the intensity will continue for 12 weeks.

Likewise, the subset of children who will have two MRI studies will be given the same standard of care for any young child undergoing these procedures. The Barrow's Neurological Institute in the Phoenix Children's Hospital has considerable experience in preforming these studies and the children will under the care of certified anesthesiologists. If anything unforeseen should occur, the Children's Hospital is fully staffed and equipped to respond in the appropriate professional manner.

4.1.3 Potential Benefits of the Proposed Research to Human Subjects and Others

• Potential benefits of the research to research participants and others

With the intensity with which the therapies are being given, it is anticipated that the gains the young child will make with therapy will occur at a faster rate than if the therapies were given less frequently. The risks are minimal and the potential benefits large not only to the children enrolled in this study but potentially to the larger population of children with cerebral palsy.

4.1.4 Importance of the Knowledge to be Gained

• Importance of the knowledge to be gained

This proposal seeks to evaluate an approach to a condition currently managed with less than optimal results in the U.S. It is one more step in the evolution of developing better care for children with CP. As such, we expect it to have impact at multiple levels:

- At the patient level: If our hypotheses prove true, the findings might have important and far-reaching implications for the treatment of children with spastic CP. If children with this condition can improve their functional abilities through intensely administered therapies, their degree of independence will increase and as it does, improvement in other aspects of their lives (social, emotional and employment) will be seen.
- At the sub-set level: If we are able to identify historical, functional, or radiographic factors that predict response to intense early therapy, it would help direct optimal provision of services for maximum benefit and cost effectiveness.
- At the health policy and economy levels: A decrease in morbidity will lessen the tremendous burden of healthcare expenditure that is currently estimated at a lifetime cost of $921,000 per person with CP. Initiating intense therapies early has the potential of preventing at least some of the surgical procedures now being performed in the U.S. each year for children with CP.

• The risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

The risks are minimal and the potential benefits large.

4.1.5 Data and Safety Monitoring Plan

This study meets the NIH definition of a clinical trial. Therefore, it is our intention to create a three member Data Safety and Monitoring Board of persons not affiliated with the research project in addition to PI and the Co-PI. Names will be submitted to U of Arizona's Institutional Review Board (UAIRB) for approval. The DSMB will be created prior to the beginning of the study and will consist of at least two individuals outside of our program and a third who is outside of our institution. One of these individuals will have statistical expertise. Prior to initiation of the trial, the DSMB will approve the consent form. The DSMB will meet once a year and have interim conference calls if needed. Official minutes will be taken by the project statistician, Dr. Chengcheng Hu, and will be forwarded to the UAIRB after each meeting. The major functions of the DSMB will be to review project performance and monitor patient safety. The DSMB will review recruitment and data collection to ensure that the project goals are met. The DSMB will also approve all changes to the protocol. At its initial meeting, members of the DSMB will decide what data points they need to monitor to ensure patient safety and if they need a priori stopping rules or guidelines.

At each meeting, the DSMB will vote whether to continue the trial. Reasons for early termination of the trial may include concerns about safety of the treatments, an early convincing beneficial effect of treatment, or such poor performance by the investigators that successful completion of the trial is unlikely. The DSMB may also recommend amendments to the study protocol if it appears they are necessary for safety or scientific validity of the trial.

A special responsibility of the DSMB is to review serious adverse events (SAEs), as defined by deaths, life-threatening conditions, hospital admissions, serious injuries, or events that require the permanent discontinuation of the intervention. No SAEs are anticipated as the intervention is using standard therapies that have been administered to children with cerebral palsy. It is only that they will be administered at a greater frequency than is the current standard of care. However, should a SAE occur, it will be reported to the U of Arizona's Institutional Review Board in the standard manner with follow-up reporting until the event has terminated. SAEs will be reported to the DSMB by the procedures they determine.

4.2 Inclusion of Women and Minorities

This is a study that is designed to investigate the efficacy of an intense series of physiotherapies on children between the ages of 12 and 36 months with cerebral palsy. No one older than 36 months at the time of enrollment is eligible to participate in the study. Any child of either gender and regardless of ethnicity who meet the eligibility criteria may be enrolled.

Program Director/Principal Investigator (Last, First, Middle):

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Intense physiotherapies improve function in children with cerebral palsy

Total Planned Enrollment: 110

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	12	18	30
Not Hispanic or Latino	32	48	80
Ethnic Category: Total of All Subjects *	44	66	110
Racial Categories			
American Indian/Alaska Native	1	1	2
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American	2	3	5
White	41	62	103
Racial Categories: Total of All Subjects *	44	66	110

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

4.4 Inclusion of Children

• Plans to include children

This proposal is designed to determine the efficacy of an intense series of physiotherapies on children between the ages of 12 and 36 months with a diagnosis of cerebral palsy (CP). The rationale for this age group is based on the fact that the diagnosis of cerebral palsy is often uncertain under the age of 12 months especially in prematurely born infant. The cutoff of 36 months is to have a homogeneous population of young children when the brain is most 'plastic' and most susceptible to reorganization. In addition, these children are not yet in school and would not have to miss typical activities, are frequently in home-based care situations that facilitate daily therapy attendance, and this is an age at which motor progress is generally recognized, and the evaluation tools we will be using are validated for children to 36 months and beyond.

The insult to the CNS that caused CP must have occurred during gestation or within one month after birth and may be associated with prematurity but not due to neuronal migration. Although there is no consensus regarding a specific cutoff time for the injury that caused CP to occur and frequently one cannot be definitive on the time of insult, the cutoff of one month will be used for each subject.

Only children with CP of a severity level I, II, and III will be considered. The level of severity will be based on the Gross Motor Function Classification System (GMFCS). Children with levels IV and V, more severe CP will not be included.

All co-morbidities will be considered, unless they a) are considered contraindication for rehabilitation therapies and/or b) may compromise our ability to maintain blind evaluations, and c) are of a serious nature not typically associated with CP (i.e. cancer, cystic fibrosis).

Children whose parents/caregivers will not consent to not altering the dose of any anti-spasticity medications their child may be on and will not consent to not providing their child with any formal CP-related therapy during the 48 week protocol.

Children who are participating in another CP trial that potentially might conflict with this trial will be excluded.

Qualified Personnel

Dr. Duncan, the PI on this project has been caring for children for over 50 years, most of that time caring for children with special health care needs. Currently he is a Professor Emeritus but formerly was a Professor of Pediatrics and Public Health. He understands that one of his chief responsibilities is to insure that the research is conducted in a way that respects the rights and safety of all enrolled participants and is in accordance with the institutional policies of the State and the University of Arizona. It is his job to supervise the study personnel making sure that those hired are qualified to perform the tasks they are assigned, that they have a clear understanding of the project, that they adhere to the study protocol, that they realize the importance of immediately reporting any adverse or unanticipated problems, and that they respect the confidentiality of the families enrolled. He will be the direct liaison to the Data and Safety Monitoring Board and will keep the Board informed as to the progress of the study and when and if any adverse problems arise. He is responsible for ensuring that no child begins an

evaluation or enters therapy until the consent has been signed and that the randomization and stratification is conducted as planned.

Dr. Brandys, the Co-Investigator at the Phoenix Children's Hospital has been caring for children for more than 25 years. Before coming to the United States, she had extensive training in pediatric rehabilitation in Poland which was followed by additional post doc training in Physical Medicine Rehabilitation at the Hospital of the U. of Pennsylvania in Philadelphia and then a fellowship in Pediatric Rehabilitation Medicine at The Johns Hopkins University School of Medicine in Baltimore. In Poland, the standard of care for children with cerebral palsy is not much different from what this project will evaluate using sound scientific methods. She is an ideal person to oversee the clinical aspects of this project and will do that both at the Phoenix Children's Hospital and at the Tucson Medical Center.

Facilities

The facility in Phoenix is the ambulatory unit of the Phoenix Children's Hospital and has all the necessary equipment and personnel to care for any adverse event that may occur.

The facility in Tucson is the outpatient pediatric therapy center of the Tucson Medical Center and that Hospital has all the necessary equipment and personnel to care for any adverse event that may occur.

1.14 Multiple Project Director/Principal Investigator (PD/PI) Leadership Plan

Rationale for choosing a multiple PD/PI approach: Our intension is to conduct, from cerebral palsy study standards, a very large investigation involving both a clinical assessment and an anatomical (MRI/Diffusion Tension Imagining) assessment. The population of Tucson is a little over 500,000 with a little over 1 million in the greater metro area. We felt it was problematic that the Tucson area alone could recruit and enroll a sufficient number of children with cerebral palsy between the ages of 12 and 36 months whose families could commit to the intensity of the therapies proposed in this study. That was the principal driving forces for choosing a multiple PD/PI approach. In expanding the investigation to Phoenix with a population close to 1.5 million and 4.3 million in the metropolitan area, the potential enrollment was greatly increased. Adding the research expertise of Dr. Jorge Arango at the Barrow's Neurological Institute in Phoenix Children's Hospital as Co-PI greatly advanced the investigative team. In addition, the clinical expertise and experience of Dr. Ewa Brandys as a Co-Investigator brought an important complement to the research experience of Dr. Duncan and Dr. Arango.

Until 2007, the University of Arizona's (U of A) College of Medicine located in Tucson was the only medical school in Arizona. In 2007, the U of A opened a campus for a four-year medical degree program in Phoenix. The two medical colleges are collaborating in a diversity of research projects and the climate is encouraging for cooperating in joint ventures. Dr. Duncan is a Professor Emeritus and as the reviewers can easily calculate, is past retirement age but he is in excellent health (vitamins are his only medication), has no plans on stopping work, and currently maintains a ± 60 hour week schedule. However, it was thought prudent that a younger person(s) be intimately involved at the earliest stages and highest level in planning and implementing the investigation. That fit in nicely with expanding the project to the Phoenix Children's Hospital.

The Outpatient Therapies facility at the Tucson Medical Center (TMC) is a premier rehabilitative unit for children in Tucson and the therapists there see many of the youngest children with cerebral palsy who live in Tucson. Many more children are seen for rehabilitation services at this TMC facility than at the University of Arizona Medical Center. Marylou Fragomeni, a speech therapist and manager of pediatric therapies at TMC has been working with Dr. Duncan for many years. Most recently they have collaborated on a feasibility study that enrolled 18 children between the ages of 18 and 36 months in a cerebral palsy study. That study was designed to see if families of a child with cerebral palsy would/could follow the rigor of the intense therapies as proposed in the investigation being submitted to the NIH. The compliance rate for the families of the children enrolled was 82% and the children showed a significant improvement in function as measured both by the GMFM-66 and the PEDI. Ms. Fragomeni is employed full-time by TMC and it is her responsibility of overseeing the therapy provided by her staff regardless of who is paying for them. For that reason, she has not requested any additional funds from this grant. The Project Coordinator in Tucson will assist her and the staff there with the scheduling of therapy and evaluation appointments and she/he will insure that the families are reminded of the times when they are to be seen.

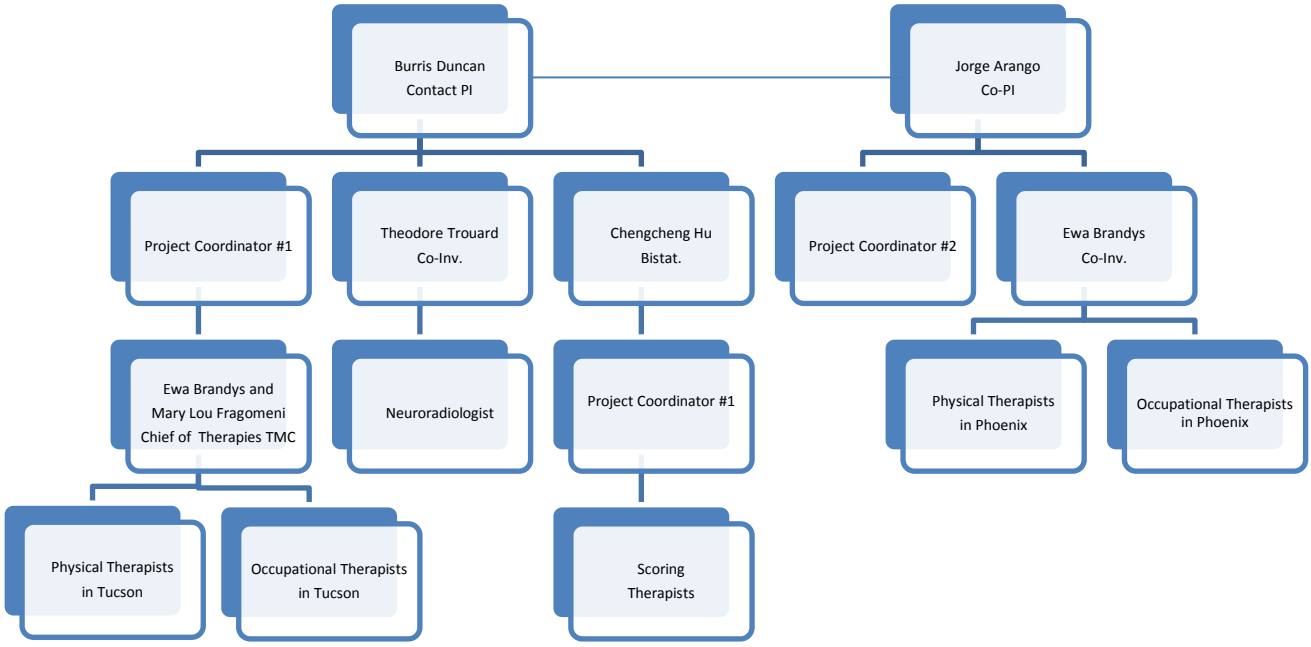
The governance and organizational structure: Over the past 12 months since this project was first introduced to Drs. Arango and Brandys by Dr. Duncan, the three individuals have been in frequent contact with telephone conversations, on-site visits, and email exchanges with every aspect and step of development of the proposal. Numerous visits have been made to the Phoenix Children's Hospital by Dr. Duncan and Dr. Brandys' has made collateral visits to Tucson. These three key persons have developed a close working relationship with open and frank discussions. Dr. Chengcheng Hu has been engaged as the biostatistician and

methodologist. Dr. Hu is employed at the Mel & Enid Zuckerman College of Public Health that has programs in both Tucson and Phoenix. Dr. Hu works with the programs in both cities and has one office in Tucson and another in Phoenix. This puts him in an ideal position to oversee the technical aspect of the project at both sites and to insure that communications are frequent, transparent, and any conflicts identified early and resolved quickly.

The theoretical framework (Perception Action) that will govern the physiotherapies is a well-accepted approach that has been the operational modality at the Outpatient Treatment facility at the TMC for over eight years. The therapists in Phoenix have been trained in this approach and have agreed to adopt it for this study. Dr. Brandy will insure that this approach is administered appropriately by the therapists at both sites in as close to an identical manner as possible.

The Tucson PI and/or the Tucson Coordinator will travel to Phoenix at least once a month during the entire five year grant period; a total of at least 60 round trips between Tucson and Phoenix. These frequent visits will insure that the protocol is adhered to and any technical or scientific problems are identified early and discussed jointly with Dr.Hu. In addition Dr. Brandys will travel from Phoenix to Tucson on a periodic basis to insure that the therapies are progressing well and that the therapists at the two sites are consistent in the administration of the therapies.

Organizational structure will be similar at the two sites



Each of the three institutions (U of A, TMC, and PCH) has its own IRB and approval will be obtained from each. In addition, a Data and Monitoring Board will be developed specifically for this project with the purpose of making sure no adverse incidents occur or if they do that each is rapidly addressed and resolved.

The principal contract will be with Sponsored Projects at the U of A where administrative and budgetary matters of the entire project will be handled. A sub-contract has been made with Phoenix Children's Hospital and the Tucson Medical Center. The respective administrators will oversee their own portion of the budget and will report to the U of A Sponsored Project administrators.

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PHOENIX CHILDREN'S Hospital

STATEMENT OF INTENT TO ESTABLISH A CONSORTIUM AGREEMENT

Date: May 20, 2013

Grant Number (if available):

Application Title: Intense physiotherapies to improve function in young children with cerebral palsy

Proposed Project Period: 04/01/2014-03/31/2019

The appropriate programmatic and administrative personnel of each institution involved in this grant application are aware of the (NIH, NSF, etc.) grant policy and are prepared to establish the necessary inter-institutional agreement(s) consistent with that policy.

ARIZONA BOARD OF REGENTS
UNIVERSITY OF ARIZONA

Signature Date
Principal Investigator

Leslie P. Tolbert
Vice President for Research

PHOENIX CHILDREN'S HOSPITAL, INC.

Dr. Ewa Brandys
Principal Investigator

Robert Meyer
President and CEO

Tucson Medical Center

STATEMENT OF INTENT TO ESTABLISH A CONSORTIUM AGREEMENT

Date: 05/27/2013
Grant Number: PA-11-260
Application Title: Intense physiotherapies to improve function in young children with cerebral palsy
Proposed Project Period: 4-1-14 to 3-31-19

The appropriate programmatic and administrative personnel of each institution involved in this grant application are aware of the (NIH, NSF, etc.) grant policy and are prepared to establish the necessary inter-institutional agreement(s) consistent with that policy.

ARIZONA BOARD OF REGENTS
UNIVERSITY OF ARIZONA

_____

Signature Date
Principal Investigator

_____

Leslie P. Tolbert
Vice President for Research

Tucson Medical Center
Outpatient Therapies

_____

Signature Date
Principal Investigator

Alicia Kang MSN RN 5/28/13

Director, Women's and Children's Services
Tucson Medical Center

PHS 398 Checklist

OMB Number: 0925-0001

1. Application Type:

From SF 424 (R&R) Cover Page. The responses provided on the R&R cover page are repeated here for your reference, as you answer the questions that are specific to the PHS398.

* Type of Application:

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

Federal Identifier: Grant11410563

2. Change of Investigator / Change of Institution Questions

☐ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:
* First Name:
Middle Name:
* Last Name:
Suffix:

☐ Change of Grantee Institution

* Name of former institution:

3. Inventions and Patents (For renewal applications only)

* Inventions and Patents: Yes ☐ No ☐

If the answer is "Yes" then please answer the following:

* Previously Reported: Yes ☐ No ☐

4. * Program Income

Is program income anticipated during the periods for which the grant support is requested?

☐ Yes ☒ No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

*Budget Period	*Anticipated Amount ($)	*Source(s)

5. * Disclosure Permission Statement

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

☒ Yes ☐ No