# NINDS/NICHD Strategic Plan for Cerebral Palsy Research

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# Introduction

Cerebral palsy refers to a group of disorders affecting movement, muscle tone, and/or posture that result from damage to the developing brain, most often before birth.  The degree of motor impairment and extent of comorbid non-motor conditions varies across affected individuals.  While the brain damage that leads to cerebral palsy is not progressive, motor and other impairments may evolve over time because of ongoing plasticity and adaptation.  The mechanisms that lead to cerebral palsy are not fully understood, but possible associated factors include low weight for gestational age or premature birth, maternal or neonatal infections, perinatal stroke, hypoxic-ischemic encephalopathy, early childhood traumatic brain injury (TBI), and genetic susceptibilities. Cerebral palsy is common, with an estimated prevalence in the US of around three per 1000 children[1]. About one third of cerebral palsy cases occur in infants born prematurely.

Congressional report language to the National Institutes of Health (NIH) requested a 5-year strategic plan for research on cerebral palsy.  In response, the National Institute of Neurological Disorders and Stroke (NINDS) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) held two workshops which brought together scientists, clinicians, and advocates for individuals affected by cerebral palsy.  Based on the workshop discussions, a set of high priority recommendations were identified and classified into three main areas: basic and translational research, clinical research, and workforce development.  These recommendations were shared with the workshop participants and the advisory council to NINDS, and they were posted for broad public comment between March 15 and April 7, 2017.  The final NINDS/NICHD Strategic Plan for Cerebral Palsy Research presents these recommendations as a collective vision for the entire cerebral palsy research community to advance together over the next 5-10 years.

# Background

During the appropriations process for Fiscal Year (FY) 2017, Senate report language urged the National Institutes of Health (NIH) to work with scientists and stakeholders to develop a 5-year strategic plan for research on cerebral palsy prevention, treatment, and cure through the lifespan with the goal of reducing the number of people impacted by cerebral palsy overall, as well as improving the treatment, and opportunity for recovery of those already diagnosed.

To support the development of a strategic plan, two workshops were convened at NIH in Rockville, MD.  Both workshops were co-sponsored by the NINDS and NICHD.  The first meeting received additional support from the American Academy for Cerebral Palsy and Developmental Medicine, the Cerebral Palsy International Research Foundation (subsequently known as the Cerebral Palsy Foundation), and Reaching for the Stars.  The second meeting also received support from the Cerebral Palsy Foundation.

The first meeting, on the State-of-the-Science and Treatment Decisions in Cerebral Palsy, occurred on November 12-13, 2014.  The goals of the meeting were to discuss issues, including 1) Current practices in preventing, diagnosing, and treating cerebral palsy and assessing the types of impairments; 2) Variability in clinical cerebral palsy management and treatment from infancy through adulthood; 3) Current state of the evidence base; 4) Existing registries and surveillance activities; and 5) Unique needs of adults with cerebral palsy.

The second meeting, on Basic and Translational Research in Cerebral Palsy, occurred on March 24-25, 2016.  The goals of this meeting were to assess critical gaps in practice and research, and to discuss issues, including 1)

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[1] *Data & Statistics for Cerebral Palsy*, Centers for Disease Control and Prevention, 2016, https://www.cdc.gov/ncbddd/cp/data.html. Accessed February 16, 2017.

Research performed in model systems and the relevance to cerebral palsy and therapeutic development, 2) Potential neuroprotective and reparative strategies for cerebral palsy, 3) Appropriateness of neuroimaging biomarkers for cerebral palsy diagnosis, and 4) Potential use of interventions promoting neuroplasticity to improve function in cerebral palsy. Publications detailing the discussion from each workshop are available[2] and in preparation, respectively.

High priority recommendations that emerged from these workshops form the backbone of this strategic plan to guide cerebral palsy research over the next 5-10 years. Basic research followed by clinical trials have led to preventative measures that have decreased the burden of illness due to cerebral palsy. These include measures to prevent premature birth, intrapartum magnesium treatment in premature delivery, and treatment of hypoxic/ischemic encephalopathy at birth with hypothermia. Indeed, trials are now ongoing to further protect the brain of high risk infants. Despite these advances in public health, many children still suffer brain injury in utero or at birth. This strategic plan for cerebral palsy research focuses primarily on understanding etiology and pathophysiology, improving diagnosis, identifying potential therapeutic interventions, developing potential prevention strategies and improving quality of life in affected children and across the lifespan. It is anticipated that patient-oriented outcomes will also be a key element of future cerebral palsy research efforts.

# Recommendations

## Priority Area 1 – Basic and Translational Research

### *Enhance understanding of the fundamental mechanisms of the developing brain-spine-muscle axis*

**Recommendation 1 – Create and evaluate multiple animal models to study different mechanistic and developmental aspects of cerebral palsy.**

The developing nervous and muscular control systems have intricate spatial and temporal genetically driven patterns that ensure proper control of motor function. The full scope of developmental mechanisms for normal function of this system, let alone during disrupted conditions, such as cerebral palsy, are poorly understood. Further investigation into the normal development of this system is needed.

In addition to investigating normal developmental mechanisms, more emphasis is needed to elucidate the complex dynamic created when environmental perturbations, e.g. ischemia or perinatal stroke, inflammation or nutritional status and low gestational body weight, impinge on the neurodevelopmental program for the brain, spinal cord and musculoskeletal systems. Empirical models that capture the complexities of the biology of cerebral palsy would be of great value. The importance of mother's contribution to fetal health, especially placental function, cannot be underestimated as much of cerebral palsy occurs in the antenatal period, so models of both intrauterine and postnatal pathways are needed. These models should be inclusive in their scope to assess the contribution of the placenta, putative protective mechanisms, possible repair and regeneration mechanisms, the role of inflammation and immunologic processes, and genetic and genomic factors. The newly developed tools to interrogate and modulate brain circuit activity in animal models (optogenetics, chemogenetics) also offer new opportunities to examine how the insults that cause cerebral palsy

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[2] Lungu, et al. (2016). Report of a workshop on research gaps in the treatment of cerebral palsy. *Neurology*. 2016 Sep 20;87(12):1293-8. PMID: 27558377

affect the development of neural circuits, at both the brain and spinal cord levels, and how abnormal circuitry might be manipulated for functional benefit. It will be essential to consider key differences in human pathophysiology compared to the biology of empirical animal models (e.g., amount of white matter) and how these differences could affect the ability to translate findings.

### Recommendation 2 – Empirically evaluate cellular and molecular pathways of injury and repair.

Experimental models can be used to better understand processes related to cell injury, cell death and the changes that occur consequent to the injury in the developing brain. Establishing a knowledge base of how the various molecules in the microenvironment impact these processes is a critical first step to developing neuroprotective and neuroregenerative therapies.

Research should address key knowledge gaps to develop a clear understanding of the cellular changes after injury and the subsequently affected molecular pathways that can lead to cell death. Efforts should be made to identify strategies - either pharmacological, biological, or genetic - that may reverse damage induced by cerebral palsy-related neurodevelopmental insults. Engagement of repair mechanisms, including neurogenesis or neuroplasticity, should be examined to facilitate recovery or compensatory remodeling of important neural circuits in the brain and spinal cord.

### Recommendation 3 – Study cell-based therapies.

Rigorous evaluation of preclinical and clinical outcomes is essential to evaluate the effectiveness of stem cell therapies. Reports of uncontrolled trials utilizing a variety of different types of stem cells administered in various ways from groups outside the US are difficult to interpret.

The basic understanding of how endogenous or exogenous neural progenitors contribute to functional recovery in the injured, developing nervous system is very incomplete. Research is needed to understand whether and how stem cell-based therapies can be productively used to treat persons with cerebral palsy. Important considerations include how stem cell-therapies integrate into neural circuits and/or enhance endogenous repair mechanisms in the specific types of injury that underlie cerebral palsy. Rigorous research is needed to clarify the relevant parameters for stem cell therapy, such as stem cell type; impact of adding growth factors; need for concomitant immunosuppressive treatment; as well as the timing, dosage, location and method of administration. To guide human clinical trials, it will be necessary to learn how to track the intended effects in the short- and long-term, as well as the risks versus benefits across development.

While research into neuroprotective, neuroreparative and stem cell therapies administered to affected individuals is critically important, development of therapies that may be administered maternally could hold promise but require substantial additional investigation.

## *Integrate state-of-the art neuroimaging*

### Recommendation 1 – Broaden application of current advanced neuroimaging techniques.

Brain injury that underlies cerebral palsy causes a widespread disturbance in neuronal connectivity that extends beyond a single, primary locus and may include synapses in the ischemic penumbra, or in brain/spinal cord locations that are connected to the injured region. Advanced neuroimaging and neurophysiological mapping techniques offer the potential to identify not only the extent of structural injury but also the effect that this injury has on widely dispersed neural circuits.

Comprehensive methods can investigate whole-brain connectomics using diffusion tractography and resting state BOLD functional imaging.  Neurophysiologic studies using trans-cranial magnetic stimulation can interrogate inhibitory and excitatory processes.  Metabolic imaging, task-dependent functional imaging, and longitudinal imaging across the whole life course may offer further insights into the circuit disturbance in persons with cerebral palsy.  Whole-body imaging should also be explored, shifting the focus beyond the brain to include the placenta of the mother as well as the spinal cord, peripheral nervous system, and neuromuscular system, in particular descending motor pathways of affected individuals.  To support these imaging practices, MRI technology should continue to be advanced to improve functional and structural resolution.  Comparison of connectome data from affected individuals can now be compared to a large library of normative data collected as part of the Human Connectome/Lifespan Connectome project (http://lifespan.humanconnectome.org/).

## Recommendation 2 – New technologies for fetal and perinatal brain evaluation.

Non-invasive fetal neuroimaging is a promising tool that could yield valuable biomarkers of those insults that occur in the ante-natal period.  In utero resting state fMRI has the potential to map the development of brain functional connectivity before birth, and therefore holds promise of being able to detect abnormal connectivity due to fetal brain insults that occur during pregnancy.  In all infants, perinatal hypoxia/ischemia and chorioammionitis are significant risk factors for cerebral palsy.  New technologies with improved sensitivity and specificity to detect overall fetal wellbeing, including repeated assessment of placental functions for clinical decision making has the potential to improve neurological outcomes, including implementation of neuroprotective therapy when needed.  As part of developing new technologies, consideration of the safety of the new technology and potential requisite contrast agents is an essential element in these efforts.

High-resolution structural imaging in concert with resting state functional MR imaging could identify brain abnormalities in cortical and white matter development in the high risk premature or term infant in addition to functional connectivity analyses of MRI (fcMRI) signals, near infra-red spectroscopy-based diffuse optical tomography (fcDOT) can also measure the temporal correlations in low frequency fluctuations in blood oxygenation among brain regions.  fcDOT might have the ability to assess connectivity at the bedside to identify premature or term babies most at risk for neurodevelopmental problems.  To facilitate estimation of infant risk profiles, collaborations should be fostered between neuroimaging researchers and placenta scientists to identify placental pathology that may contribute to the insults that cause cerebral palsy.

## Recommendation 3– Integrate imaging throughout basic to clinical investigations.

Traditional MRI findings of brain injury in cerebral palsy, such as gyral anomalies or periventricular leukomalacia (PVL), are not comprehensive biomarkers, and currently underestimates the impact of PVL on more extensive networks and circuits due to a concomitant impact on gray matter.  In addition, neuroimaging in isolation is insufficient; it needs to be linked to neurodevelopmental outcomes.

Structural and functional imaging should be combined, allowing for quantitative cross-mapping of markers such as functional MRI (fMRI) of neural activation with diffusion tensor imaging (DTI) of fiber track connectivity.  Multidisciplinary approaches should be used to combine MRI, and even other types of imaging (*e.g.*, fNIRS), with behavioral, electrophysiological, and/or clinical outcomes such as spasticity, dyskinesias and motor control, epilepsy, intellectual impairment, speech impairment, and sensory function, as well as with histopathological measures.  This approach will enable understanding of how developmental and neuroprotective interventions affect functional brain development.

## *Clarify mechanisms and establish biomarkers*

### Recommendation 1 – Identify mechanistic basis of genetic, structural, and functional factors that drive impairment and recovery.

The conceptualization of cerebral palsy as a non-progressive disorder is outdated.  Instead, in the context of ongoing neuroplasticity cerebral palsy is ever-changing.  It is critical to know whether interventions during the perinatal period or thereafter can take advantage of intrinsic mechanisms to enhance repair, stimulate compensatory processes for functional benefit, and inhibit those that lead to functional disability; spasticity and epilepsy as prime examples.  To productively intervene, improved understanding of how cellular connections are modified by the injury and in post-injury periods is needed.

One key area of investigation is susceptibility to injury, including the relative roles of vascular and circulatory factors and inflammation.  Another major issue is the bidirectional relationship between genetics and injury, in particular the genetic predisposition to injury response and how injury alters genetic programs through epigenetics.  A further issue is to understand how the injuries that cause cerebral palsy also lead to hydrocephalus, especially after intraventricular hemorrhage in premature infants.  Because not all perinatal brain injuries lead to cerebral palsy, a third issue is comprehending the resilient phenotype and how it can be promoted.

Partly because of the potential interactions between genetic risk and epigenetic response to injury, investigations focused on the genomic/genetic factors that contribute to the etiology of cerebral palsy are needed for a full understanding of the pathobiology of cerebral palsy.  In addition, sex-based differences are known to exist, but remain understudied.

### Recommendation 2 – Develop human cerebral palsy biomarkers.

Cerebral palsy is heterogeneous with respect to both types of injuries and responses to injuries.  Biomarkers assessing status of the brain and spinal cord structure and function and immune system response could help improve diagnostic accuracy, explain heterogeneity, and assist prediction of treatment outcomes.  Leveraging biomarkers for early diagnosis of cerebral palsy is an important facet of this effort.

Biomarkers should be developed that are biologically relevant, reliable, feasible, and readily available (e.g., blood, amniotic fluid, neuroimaging, CSF, neurophysiological).  Biomarkers of risk or resilience should be based on trajectories (i.e., not static measures) as a phenotypic bridge between genes and behavior.  Biomarkers should be monitored in real-time to identify onset, progression, and severity of early injury as well as response to intervention.  To inform clinical trials, it would be valuable to develop biomarkers of target engagement or proof of biologic principle that are useful in the relatively short-time period of a phase 2 clinical trial (e.g., 6 months to two years).  If such biomarkers were also predictive of long term benefit that would be ideal.

## *Understand and utilize neuroplasticity*

### Recommendation 1 – Identify critical periods of brain and motor development.

Neurophysiological processes that occur post-injury are potential targets for early intervention and prevention efforts.  Research efforts should clarify key processes that occur during this period, which include synaptogenesis and synaptic pruning to promote neuroplasticity, immune system development to normalize immune response, and bidirectional effects between brain activation and muscle metabolism to improve motor function.  Because cerebral palsy may not be diagnosed until after critical periods have elapsed, consideration should be given to how identification of critical periods can translate to clinical applications.

The singular event that initiates brain injury may be followed by other events, which may not be noticeable for some time, such as the development of spasticity, epilepsy, progressive musculoskeletal impairment or epigenetic dysfunction leading to abnormal immune response in older children.  Intervention during the acute, subacute, and repair phases following injury could possibly prevent these tertiary mechanisms that contribute to the long-term disability in persons with cerebral palsy.  The heterogeneity of cerebral palsy suggests a multifactorial etiology and may require a multidimensional therapeutic strategy.

A deeper understanding of the biology of non-invasive neuromodulation and neurostimulation techniques should be sought to determine the appropriateness of deploying these technologies in the treatment of cerebral palsy across the lifespan.

**Recommendation 2 – Consider neuroplasticity-promoting interventions from other fields.**

Collaborations should be fostered with other clinical fields that involve brain damage (e.g., stroke, traumatic brain injury, post-surgical resection).  The existing literature and clinical practices in these fields may inform cerebral palsy prevention and treatment methods across the lifespan.

An interdisciplinary approach should be adopted to identify translatable lessons, including how to integrate clinical care and research, provide opportunities for intensive practice during rehabilitation, and promote development and plasticity throughout the lifespan of those affected by cerebral palsy.  However, consideration should be given to the potentially limited applicability of knowledge from adult rehabilitation to pediatric cerebral palsy and the challenges inherent in adapting interventions for this population to children.


# Priority Area 2 – Clinical Research


## *Consider the entire lifespan*

**Recommendation 1 – Improve precision diagnosis and treatment at the level of an individual.**

Early interventions to minimize early effects of injury on body structure and function are intended to improve abilities in functional activities, with the goal of enabling increased participation in society and promoting independence.  Successful outcomes are considered more likely if diagnosis and intervention both occur early.

Diagnostic measures should be improved to enable an earlier and more accurate diagnosis.  However, because there are many transient motor impairments that can appear in infancy and early childhood, consideration should be given to the reliability of the diagnosis and the potential consequences of an early, but inaccurate, diagnosis.  To disambiguate between cerebral palsy and transient motor disorder, it may be particularly valuable to examine biomarkers (see page 6, *Develop human cerebral palsy biomarkers*); genomic, epigenetic, and metabolomics information; and early clinometric measures.

The variability of cerebral palsy manifestations makes intervention and treatment particularly challenging.  By improving earlier personalized diagnosis, researchers and clinicians may be able to personalize intervention strategies that maximize effectiveness.  Individuals with cerebral palsy also experience coexisting conditions that increase the challenge of living with this disorder.  Effective treatment strategies are needed to mitigate co-occurring conditions, such as pain, cognitive impairment and mental health concerns in cerebral palsy.

There is a need to examine cerebral palsy in diverse populations to determine potential differences in risk factors contributing to the etiology of cerebral palsy.  In addition, disparities in diagnosis, care delivery, and outcomes across different populations have been under-investigated.

**Recommendation 2 – Guide newly affected families.**

Some families, especially those in under-resourced areas, do not have access to healthcare providers who are familiar with cerebral palsy. They may receive little to no information on what to do or expect after a child receives a diagnosis of cerebral palsy. Because earlier intervention has increased potential for positive impact, a structured resource could help families use their time more effectively. In addition, providing resources to caregivers and families that improve coping strategies may have long-term benefits. Enhancing the ability to access these resources from mobile devices, such as phones and tablets, could improve the use of this information.

A comprehensive "100-day kit" should be produced for families with children who are newly diagnosed with cerebral palsy, so that families can access the information they need to guide their child's care. The kit can be modeled after what is similarly available for a diagnosis of autism spectrum disorder. This resource should be easily understandable, actionable, and widely disseminated.

**Recommendation 3 – Leverage neuroplasticity.**

The brain is "plastic," as evidenced by interventions that can improve certain functions (e.g., motor skills, speech, and cognition). The concept of activity-dependent synaptic plasticity should be used to remodel circuits, specifically to restore motor function by strengthening impaired projections while preventing maladaptive plasticity (i.e., spasticity). Neurophysiological monitoring and neuromodulation approaches could be tested to facilitate rehabilitation. In particular, non-invasive methodologies, such as transcranial direct current stimulation and transcranial magnetic stimulation, require further exploration and development.

New technologies to assay brain circuitry coming from the US BRAIN initiative may be able to transform our understanding of how brain circuits develop in animal models of cerebral palsy as compared to typical developing controls. Next generation neuroimaging research and new brain recording and modulation technologies may also demonstrate promise in persons with cerebral palsy to chart how circuit function can be manipulated for clinical benefit.

Treatment approaches should take advantage of the possibility of change at any developmental level. Accordingly, efforts should be made to remove impediments to learning and to facilitate learning by enhancing brain plasticity (e.g., task-specific training, device-augmented strategies, and combination of rehabilitation with neuromodulation and/or medication). Promising methods that use this approach include motor learning (e.g., constraint-induced movement therapy); cognitive and behavioral learning; and use of exoskeletons, virtual reality, and visualization as training tools. To take full advantage of these new techniques and methods, a comprehensive understanding of the underlying basic neurobiological principles is essential.

**Recommendation 4 – Consider needs of adults with cerebral palsy.**

Adults with cerebral palsy are more numerous than children with cerebral palsy, and they face unique issues. Due to a lack of longitudinal studies, it is unclear whether current treatments used in children are beneficial or detrimental once these individuals reach adulthood.

To achieve greatest impact, treatment priorities earlier in life should be informed by issues faced by adults. Similarly, long-term follow-up of interventions, especially those occurring in childhood or translated from other fields of adult rehabilitation (e.g., stroke, TBI), should assess impact on adult function. Research and healthcare delivery efforts should facilitate the transition from childhood to adulthood, addressing concerns such as employment, pain management, cognitive impairment, aging, women's health and quality of life. In addition, an

assessment of the morbidity and mortality of cerebral palsy in aged individuals compared to normal or other disabled populations is needed.

## Enhance treatment options

### Recommendation 1 – Consider combination therapies targeting different pathways.

Much of the current research on treatments for cerebral palsy focuses on relatively mild, unilateral cerebral palsy.  Especially for other, more severe cases, it may be insufficient to test therapies in isolation or focus on intensity of motor training as the sole approach to driving neuroplasticity.

Researchers should test multimodal treatment approaches, combining neuroscience (e.g., functional electrical stimulation), orthopedics, pharmacological treatment, and rehabilitation via both physical therapy and occupational therapy.  Some clinical trials are already underway utilizing this approach.

### Recommendation 2 – Accelerate bench-to-bedside strategies by incentivizing translation specific for cerebral palsy.

Technological and environmental modifications are highly individualized and under-researched.  Consideration should be given to how technology development can be emulated in an academic setting.

New technologies should be developed and used as interventions.  Areas to focus on include noninvasive neuromodulatory tools and methods to promote durable plasticity within the corticospinal tract, and cortical activation tools with improved spatial and temporal specificity.  Existing devices merely assist movements; devices are needed that can sense and modify the environment, based on an understanding of the underlying impairments and the importance of self-generated movements.

## Revisit and update study designs in the field

### Recommendation 1 – Consider innovative study designs that can complement randomized controlled trials (RCTs).

Although RCTs are the gold standard to test intervention efficacy, they have several limitations.  In particular, RCTs are assessments over relatively short periods of time (i.e., multiple years), while individuals with cerebral palsy change as they develop and age.

Alternative research designs should be used, including rigorous prospective data collection to identify causal effects, pragmatic trials, Bayesian trials, and data mining of electronic medical records.  The usual limitations of non-RCTS, such as inconsistent data collection, lack of pre-specified hypotheses, post-hoc analyses, poor outcome assessment should be minimized using proactive measures.  Potential approaches include employing validated patient-reported outcome measures, wearable sensors, infrastructure development and blending of clinical care with research data collection so data from medical records can be more easily accessed, aggregated, searched, and analyzed.

### Recommendation 2 – Develop major comparative effectiveness studies.

Comparative effectiveness research (CER) with extended periods of follow-up is needed to identify which of the available treatments work best and for whom and to determine the optimal timing and frequency (dosage) of treatments.  For example, unlike drugs and devices, whose approval by the Food and Drug Administration (FDA)

is contingent on demonstration of efficacy, physical and occupational therapy interventions, and even some surgical procedures, are not regulated and their effectiveness is difficult to research.

Collaborative partnerships and communication networks between patients, clinicians, and researchers should be established and leveraged to conduct CER. Existing networks, such as the PCORnet Patient-Powered Research Network (PPRN) and other established clinical networks, have activated populations of patients with known conditions and could be utilized for CER or as a model for new networks.

## Maximize potential of existing registries and databases

**Recommendation 1 – Consolidate patient registries and databases.**

Many disparate registries and databases exist, each serving different purposes. Combining them would increase the usefulness of limited data and enable identification of patterns that are not obvious from smaller patient samples.

Existing registries and databases should be consolidated to accelerate research, through easier retrieval of cases, tracking of patients and services provided, and enabling collaboration, among other benefits. Databases should include many data types (i.e., surveillance, clinical, patient reported outcomes and research data). Inclusion of data from all newborns would facilitate comparison between individuals with cerebral palsy and healthy individuals. Challenges to consolidation include identification of the purpose and owner of the data, management of access and privacy concerns, and maintenance of infrastructure in the long-term.

 **Recommendation 2 – Enhance communication between patients and researchers to generate and share data.**

Better linkages are needed between patients and researchers seeking potential participants for clinical trials and CER, and between individual researchers seeking similar data. Organizing existing clinical networks may provide a mechanism to facilitate the development of new treatment approaches and enhance engagement between patients and researchers.

Public-private partnerships should be enhanced to expand cerebral palsy communication networks and repositories, facilitating interconnections between patients and researchers. This should include infrastructure to help patients identify trials for which they are eligible and grassroots efforts to increase patient participation. Researchers should collaborate to conduct CER, design fewer clinical trials (each collecting more data), and analyze previously collected data from large studies. Harmonization of international research efforts and network opportunities could be an effective strategy to accelerate treatment development.

## Develop better data metrics

**Recommendation 1 – Refine Common Data Elements (CDEs).**

Identification of CDEs would encourage expanded use of those measures. Use of CDEs would improve consistency across registries and databases, and facilitate analysis of data collected across multiple sites.

Existing CDEs should be validated for reliability; a subset of these should be responsive to change. CDEs should be refined in collaboration with clinicians, with consideration for ways to streamline the data capture process and facilitate consistent and widespread CDE use. To complement refinement of cerebral palsy CDEs, more harmonization of classification and terminology may be appropriate.

Translational investigations and drug development could be facilitated by the adaptation of the clinical CDEs for basic science investigations.  This would bring preclinical studies into closer alignment with clinical investigations and practice.

**Recommendation 2 – Increase quality and availability of patient-reported outcomes.**

It is important to include the patient perspective in the development and use of outcome measures.  Accordingly, measures should be formulated with input and relevance to patients and families (e.g., functional outcomes).

Patient-reported outcomes should be established that are meaningful to individuals and families affected by cerebral palsy (e.g., health-related quality of life measures) and intended to complement, not replace, clinician-reported measures.  Psychometrically sound, validated, flexible, and comprehensive assessments which are feasible in children and sensitive to change (e.g., PROMIS) should be used as a framework to generate these patient-reported outcomes.

# Priority Area 3 – Workforce Development

### Recommendation 1 – Enhance training of the next generation of cerebral palsy investigators.

Proactive measures are needed to ensure an adequate number of well-trained cerebral palsy researchers in the long-term.

Support should continue for programs aimed at cultivating clinician-scientists.  NINDS programs addressing this goal include a research training program for medical residents and a national mentoring program for pediatric neurologists.  NICHD programs also address this goal and emphasize the K12 program as well as training through the Rehabilitation Research Network focusing on device development, neuromodulation, data science, clinical trials and movement simulation.  Other approaches include young investigator awards, support for pilot studies, and career development grants and opportunities for researchers in cerebral palsy-relevant fields.

### Recommendation 2 – Attract researchers to the field.

Existing researchers in cerebral palsy-relevant fields can lend diverse perspectives and skill sets to cerebral palsy research.  Promising individuals to target include bioengineers, computational scientists, basic and translational scientists, clinical trialists, comparative effectiveness researchers, implementation researchers, epidemiologists, obstetricians and placenta scientists.

Efforts should be strengthened to bring together clinicians and scientists from different fields, encourage cross-pollination of ideas and methods, and foster development of collaborative research goals.  Examples of such approaches include interdisciplinary grants; supplements for researchers in other fields to work on cerebral palsy; and mechanisms for workshops, meetings, and consortia.

### Recommendation 3 – Leverage expertise across specialties.

Translational researchers are limited in number, and those that exist tend to work in separate professional groups.

Connections between distinct fields of translational rehabilitation (e.g., stroke or athletics community) should be fostered to facilitate interdisciplinary collaboration.

# Summary

The two workshops that informed this strategic plan brought together scientists, clinicians, and advocates for individuals affected by cerebral palsy.  The overall strategy involves acknowledging that due to neuroplasticity, cerebral palsy is an ever-changing disorder, identifying key issues, and proposing approaches to address them.  Specifically, recommendations include advancing basic research in neurodevelopment and injury response to leverage neuroplasticity in the clinic; fostering networks between cerebral palsy researchers, clinicians, and patients to facilitate data collection and usage; and cultivating interdisciplinary teams of cerebral palsy investigators.  An aggressive approach should be adopted to identify translatable lessons, including how to integrate clinical care and research, determine which treatments work best for whom, and optimize treatment timing and frequency.

The cerebral palsy community has already begun working to implement the plan.  NINDS worked with the American Academy for Cerebral Palsy and Developmental Medicine (AACPDM) to develop a package of Common Data Elements (CDEs) for cerebral palsy (https://www.commondataelements.ninds.nih.gov/CP.aspx).  A recent example of an initiative beyond NIH to speed new therapies is the Cerebral Palsy Research Network (http://www.cpresearch.net/), which is developing a national registry for cerebral palsy. Moving forward, a virtual center for the rapid development of therapies for cerebral palsy is another potential approach.

This report outlines the overarching vision for the field of cerebral palsy, and will guide the community – including researchers, the NIH, and non-governmental organizations – in making progress toward the common goal of understanding causes, enhancing prevention, and improving treatments for cerebral palsy.