

UCSF

UC San Francisco Previously Published Works

Title

Cerebral palsy research funding from the National Institutes of Health, 2001 to 2013

Permalink

<https://escholarship.org/uc/item/49m5r3b9>

Journal

Developmental Medicine & Child Neurology, 57(10)

ISSN

0012-1622

Authors

Wu, Yvonne W
Mehravari, Alison S
Numis, Adam L
et al.

Publication Date

2015-10-01

DOI

10.1111/dmcn.12789

Peer reviewed

Cerebral palsy research funding from the National Institutes of Health, 2001 to 2013

YVONNE W WU¹ | ALISON S MEHRAVARI² | ADAM L NUMIS³ | PAUL GROSS⁴

1 Departments of Neurology and Pediatrics, University of California, San Francisco, CA; **2** Program in Neuroscience, University of Washington, Seattle, WA; **3** Departments of Neurology and Pediatrics, University of California, Los Angeles, CA; **4** Hydrocephalus Association, Bethesda, MD, USA.

Correspondence to Yvonne W Wu at UCSF Child Neurology, 675 Nelson Rising Lane Ste 411, San Francisco, CA 94158-0663, USA. E-mail: wuy@ucsf.edu

PUBLICATION DATA

Accepted for publication 23rd March 2015.
Published online

ABBREVIATIONS

NIH	National Institutes of Health
RCDC	Research, Condition, and Disease Categorization
RePORTER	Research Portfolio Online Reporting Tools Expenditures and Results

AIM Cerebral palsy (CP) is a poorly understood disorder with no cure. We determined the landscape of National Institutes of Health (NIH) funding for CP-related research.

METHOD We searched NIH databases Research Portfolio Online Reporting Tools Expenditures and Results, and Research, Condition, and Disease Categorization for keywords 'cerebral palsy' among all NIH-funded studies, 2001 to 2013. We classified grants by type and area of study.

RESULTS NIH funding, averaging \$30 million per year, supported clinical (\$215 million), basic (\$187 million), and translational (\$26.3 million) CP-related research. Clinical intervention studies comprised 19% of funding, and focused on treatments (\$60.3 million), early parent intervention (\$2.7 million), and CP prevention (\$2.5 million). Among grants that specified gestational age, more funds were devoted to preterm (\$166 million) than term infants (\$15 million). CP in adulthood was the main focus of 4% of all funding. Annual NIH funding for CP increased steadily over the study period from \$3.6 to \$66.7 million. However, funding for clinical intervention studies peaked in 2008, and has since decreased.

INTERPRETATION Additional research funds are needed to improve the treatment and prevention of CP. Topics that have been relatively underfunded include clinical interventions, prevention, and term infants and adults with CP.

Cerebral palsy (CP) is the most common motor disability of childhood. The population prevalence of CP in the US is 2 to 3.6 per 1000 births,^{1,2} and about 12 000 newborn infants each year will develop CP. In addition to debilitating motor and postural abnormalities, many patients also experience cognitive deficits, epilepsy, and visual and other developmental impairments.³ CP is a heterogeneous and poorly understood disorder with no cure. Medical costs for individuals with CP are estimated at \$1.2 million per person over a lifespan (2012 US currency).⁴ Each year, new cases of CP introduce an economic burden of \$1.9 billion lifetime costs in the US. Additional research is urgently needed to prevent and reduce suffering from this lifelong disorder.

The amount of public funding spent on CP research in the US is not well described. There have been no National Institutes of Health (NIH) Program Announcements or Requests for Applications that contain the words 'cerebral palsy' in their title.⁵ In 2014, the NIH held a 'State-of-the-Science and Treatment Decisions in Cerebral Palsy Workshop' to discuss gaps in CP research. To further inform discussions about research priorities, we set out to determine the landscape of NIH funding for CP research over a recent 12-year period.

METHOD

Using the online NIH search engine Research Portfolio Online Reporting Tools Expenditures and Results (RePORTER), we identified all grants funded by the NIH between 1 January 2001 and 31 May 2013 that contained the keyword 'cerebral palsy' within the grant title, abstract, and/or project terms. A study investigator (ASM) reviewed each grant abstract identified in the electronic search to determine if the research was indeed related to CP pathogenesis, prevention, treatment, or symptomatology. Grants that were considered unrelated to CP by two investigators (ASM and YWW) were excluded from further analyses, as were grants that were funded by the Food and Drug Administration or the Centers for Disease Control. Grant entries with identical serial numbers and topics of study were considered a single individual grant. We added all years of funding for any individual grant to determine the total funding allocated to that grant.

Since 2009, The NIH 'Research, Condition, and Disease Categorization' (RCDC) classification system has categorized all grants into 233 reported diseases and research areas, including CP. For the years 2009 to 2013, we reviewed all grant abstracts that were linked to the RCDC category of 'cerebral palsy', to identify additional grants

that may have been missed by the RePORTER keyword search.

Research grants were classified into one or more of four major categories: basic research; clinical research; translational research; and/or pre-clinical development of new technologies. Translational research refers to research in which findings are moved from the researcher's bench to the patient's bedside and community.⁶ Based on published consensus definitions, we defined three types of translational research: (1) basic to clinical, i.e. research that applies discoveries generated in the laboratory in preclinical studies, to the development of trials and studies in humans; (2) clinical to community practice, i.e. research that enhances the adoption of best practices in the community; and (3) cost effectiveness of prevention and treatment strategies.⁶

We further classified each CP research grant into one or more of the following general areas of study: central nervous system development, muscle, cellular mechanisms of injury, neuroimaging, genomics, biomarkers, risk factors for CP, speech/communication, research network or core facility, stem cells, quality of life, bone, and other.

We classified clinical intervention studies as being either an observational study or a clinical trial. Clinical trials were further categorized into phase I, II, or III trials, based on available information within the grant title and abstract. The type of intervention was categorized as follows: medications, orthopedic surgery, neurosurgery, cognitive/behavioral, rehabilitation, early parent intervention, neuromuscular stimulation, feeding/nutrition, prevention of CP, or other.

For each CP grant, we classified the target gestational age as preterm (<36wks' gestation); term (\geq 36wks' gestation); all gestational ages; unclear; or not applicable. When human participants were involved in the research, we categorized the patient population as follows: age under 6 years; 6 to 12 years; 13 to 20 years; 21 years or older; children of unclear age; all ages; pregnant mothers; or unknown.

We determined interrater reliability of data abstraction by calculating kappa values from two independent reviewers (ASM and ALN) who each abstracted data from 50 individual grants. The following categories revealed good to excellent ($\kappa > 0.6$) interobserver reliability: basic research ($\kappa = 1.0$), medication intervention ($\kappa = 1.0$), rehabilitation ($\kappa = 1.0$), intervention study/clinical trial ($\kappa = 0.96$), neuroimaging ($\kappa = 0.87$), muscle ($\kappa = 0.79$), bone ($\kappa = 0.81$), development of new technology ($\kappa = 0.79$), biomarkers ($\kappa = 0.73$), clinical research ($\kappa = 0.70$), genomics ($\kappa = 0.66$), cognitive/behavioral ($\kappa = 0.65$), and intracellular mechanisms ($\kappa = 0.65$). Variables with only moderate agreement included nervous system development/regeneration ($\kappa = 0.43$) and translational research ($\kappa = 0.37$). We eliminated variables with only poor to fair interobserver agreement (i.e. $\kappa < 0.35$) from further study: epidemiological study, long-term outcomes, and causal pathway category. After reviewing and clarifying discrepancies with a child neurologist (YWW), a single investigator (ASM) then completed the data abstraction for remaining grants. A child neurologist (YWW) re-reviewed

What this paper adds

- National Institutes of Health (NIH) spent \$30 million per year on research related to cerebral palsy (CP).
- Overall, NIH funding for CP research increased over the study period.
- NIH funding for clinical intervention studies has declined.

all nervous system development/regeneration and translational research grants (i.e. categories that demonstrated only moderate interrater reliability), and all clinical trials to determine phase of clinical testing.

RESULTS

We identified 489 individual NIH-funded grants from the RePORTER electronic 'cerebral palsy' keyword search, and an additional 18 grants from the NIH RCDC search for grants related to CP. Of these 507 grants, 40 (7.9%) were found upon further review to be unrelated to CP, and 12 (2.4%) grants were funded by agencies outside of the NIH. The remaining 455 grants represent a total of \$392.8 million in NIH-sponsored CP research funding. These grants span 188 organizations across 43 US states, and are led by 369 individual principal investigators.

Based on data provided in RePORTER, the majority of CP funding was devoted to traditional research grants, i.e. research projects (75%), intramural research (9%), or other research (8%); while smaller amounts of funding supported Small Business Innovative Research and Technology Transfer Research (3%), research centers (3%), and training grants (1%). Specific grant mechanisms included 'R' research grants (\$259 million, 65%), 'U' consortium grants (\$44 million, 11%), 'P' or 'M' program project or center grants (\$27 million, 7%), 'K' or 'F' training grants (\$21 million, 5%), and other grants (\$44 million, 11%).

Twenty different NIH institutes provided funding for grants relating to CP during the study period. The National Institute of Child Health and Human Development (NICHD) (\$160 million) and National Institute of Neurological Disorders and Stroke (NINDS) (\$137 million) together accounted for 76% of all CP research funding. Four other institutes each allocated over \$5 million toward CP research: National Institute of Biomedical Imaging and Bioengineering (NIBIB) (\$17.5 million); National Institute of Deafness and Other Communication Disorders (NIDCD) (\$13.9 million); National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) (\$9.5 million); and National Institute of Nursing Research (NINR) (\$5.3 million). The relative contribution of funding from other institutes was comparatively minor.

After removing \$1.4 million of funding spent on 80 scientific meetings, the remaining funds were categorized into one or more of the following non-exclusive research categories: clinical research (\$215 million, 55%); basic research (\$187 million, 48%); pre-clinical development of new technologies (\$45 million, 11%); and translational research (\$26.3 million, 7%). All translational research funds involved basic to clinical translation. We identified no CP

grants that involved clinical to community translation, and no cost-effectiveness studies related to CP.

The majority of basic science research funds supported studies of central nervous system development and cellular mechanisms of injury (Fig. 1). The majority of clinical research funding was spent on studies of muscle structure and function, neuroimaging, biomarkers, and genomics. Studies of risk factors for CP received a relatively small amount of funding compared to other types of CP research.

Studies that evaluated a clinical intervention received \$73.3 million, or 19% of all CP research funding. The following four interventions received over three-quarters of the funds (see Table I): medications (\$37.0 million); rehabilitation (\$15.3 million); neurosurgery (\$4.8 million); and orthopedics (\$3.2 million). Studies of interventions designed to prevent CP received a relatively low amount of funding (\$2.5 million), as did studies of cognitive and behavioral interventions.

Clinical interventions were evaluated in observational studies (\$38.3 million) or in clinical trials (\$35.0 million). More funding was allocated to phase I (\$11.3 million) and phase II clinical trials (\$17.6 million), than to phase III trials (\$6.1 million). We identified the following phase III clinical trials: prevention trials evaluating hypothermia,

Table I: National Institutes of Health funding for cerebral palsy research

Involving a clinical intervention, 2001–2013	
Type of intervention studied	\$ millions
Medication	37.0
Rehabilitation	15.3
Neurosurgical	4.8
Orthopedic	3.2
Early parent/home	2.7
Prevention of cerebral palsy	2.5
Feeding of nutrition	1.8
Neuromuscular stimulation	1.7
Cognitive or behavioral	0.3
Other*	3.6

*Other inventions include robotics, sexual health, pre-operative gait analysis, vibration, virtual reality, and wellness coaching.

magnesium sulfate, and Indocin+delayed cord clamping, and treatment trials evaluating home-based early intervention, constraint-induced movement therapy, and family-centered therapy. An additional \$29.3 million was spent on clinical trial infrastructure and to train investigators to perform clinical trials relating to CP.

The majority of funds (\$205 million, 52%) devoted to CP research did not have a clear gestational age focus that could be determined from the study abstract. Among

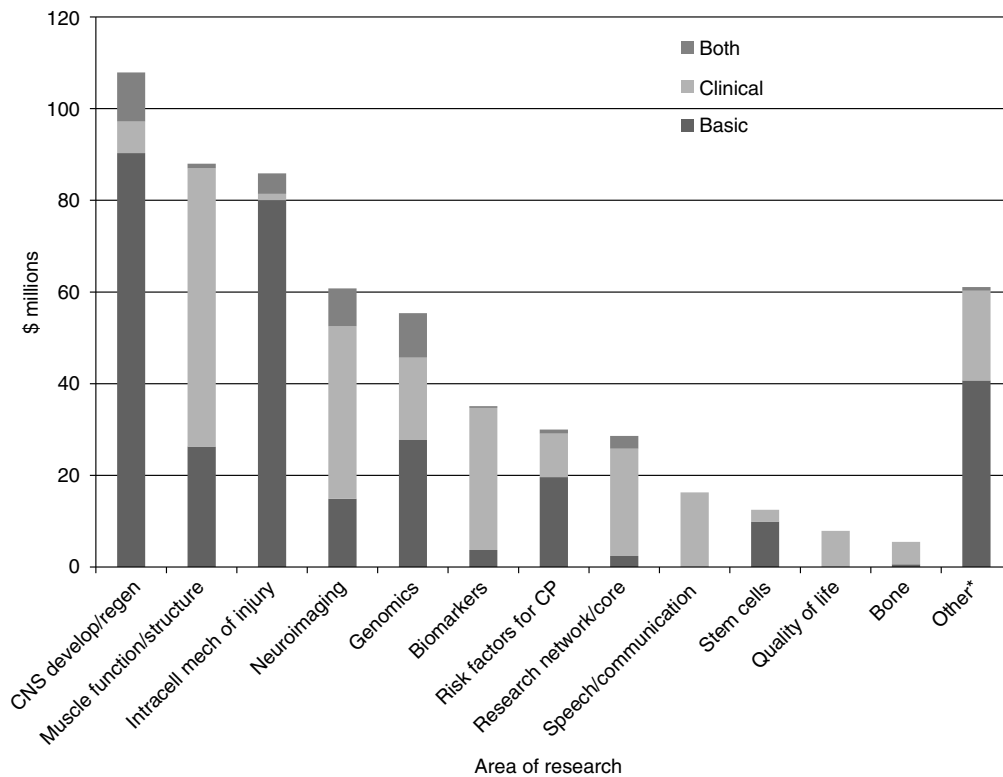


Figure 1: National Institutes of Health funding for cerebral palsy research in 2001 to 2013, by type and area of research. CP, cerebral palsy; CNS, central nervous system. *Other areas of CP research include proteomics, sleep, portion control, palliative care, pain, disaster preparedness, CP classification, aging, oral health, pain, and self-injurious behavior.

grants that specified a gestational age focus, more funding was devoted to studies of the preterm brain (\$166 million, 42%), than studies of the term brain (\$15.3 million, 4%), or to studies of CP affecting all gestational ages (\$6.5 million, 2%).

By definition, clinical studies involved human participants. About half (\$110.2 million, 51%) of all clinical research funding was spent on studies that enrolled children (participants under 21y of age.) Children under 6 years received the largest proportion of research funds,

while studies focusing on adults with CP received a relatively small amount of funding (\$8 million, 4%, Fig. 2).

NIH provided on average \$30 million a year of funding for CP research. The annual funding amount rose steadily from \$3.6 to \$66.7 million during 2001 to 2012, the years when full data were available. Increases in research funding were seen for both basic science and clinical research grants. However, studies of clinical interventions have received decreasing amounts of funding since 2008 (Fig. 3).

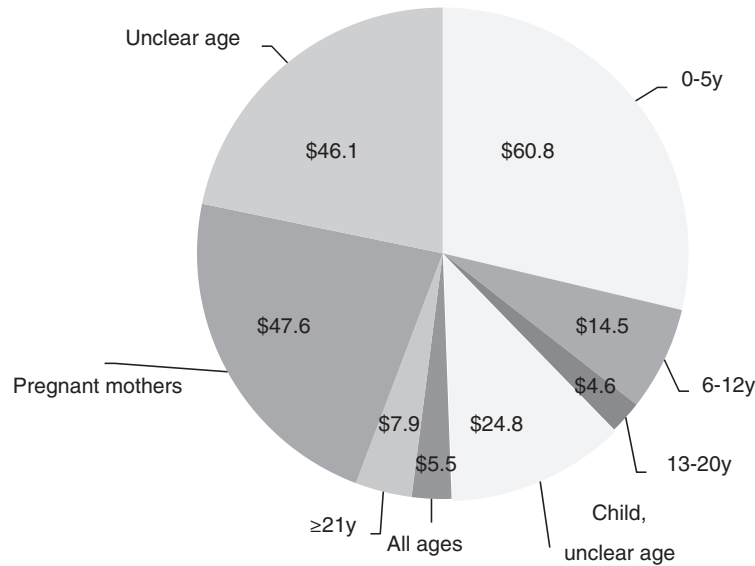


Figure 2: Age groups targeted by National Institutes of Health-funded studies of clinical cerebral palsy research.

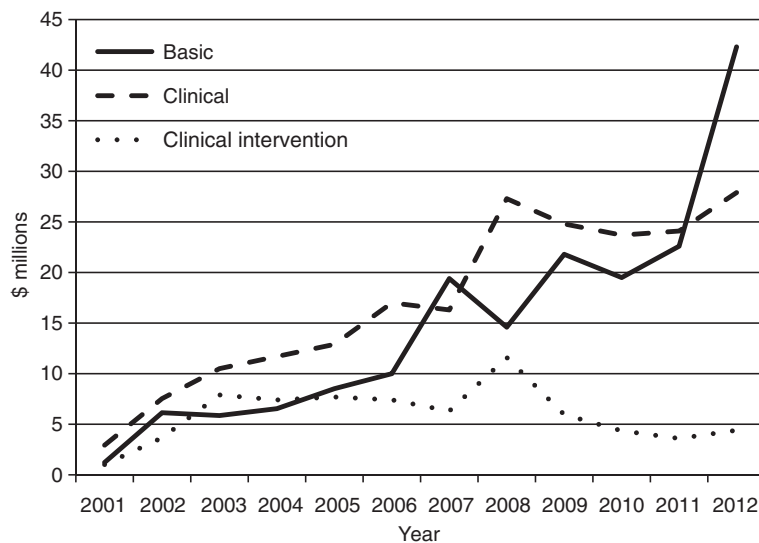


Figure 3: Time trends in National Institutes of Health funding for cerebral palsy research. The large increase in basic research funding in 2012 can be attributed to the award of a single \$21 million grant, evaluating the role of subclinical infection and cytokines in animal models of preterm delivery. Clinical intervention research is a subset of clinical research.

Starting in 2009, NIH began classifying grants using the RCDC. In the years 2009 to 2013, we identified more CP-related grants using the RePORTER keyword search than by searching RCDC. Among 267 CP grants that were funded during these years, 140 (52%) were identified both within RePORTER and RCDC; 109 (41%) were identified only by RePORTER keyword search; and 18 (7%) were identified in RCDC but not in RePORTER. Similarly, 68% of the \$218 million in NIH funding devoted to CP in 2009 to 2013 was categorized by RCDC as relating to CP.

DISCUSSION

Continued research efforts and funding are needed to develop effective strategies to prevent and treat CP. Although overall NIH funding for CP research has increased steadily since 2001, funding for studies that evaluate clinical interventions has dropped in recent years. Based on our data, specific areas of study that have been relatively underfunded include studies of clinical interventions including clinical trials, and studies of prevention of CP. Clinical to community translation studies were non-existent. Patient populations that have been relatively underfunded include term infants and adults with CP.

Our study has several limitations. Our findings are subject to incomplete ascertainment, since only grants that included the words ‘cerebral palsy’ were reviewed. For instance, our search did not identify all NIH-sponsored hypothermia neuroprotection trials, since the original grant proposals for these studies did not include the words ‘cerebral palsy’. However, among the grants we did review, all studies that could lead to information affecting prevention or treatment of CP were considered to be related to CP, even when CP may not have been the primary focus, and we identified 40% more grants that related to CP than would have been revealed by a search of the NIH RCDC categorization alone. The publicly available grant abstracts may not provide sufficient detail to allow accurate categorization of grants. We addressed this issue by having two independent observers review a subset of grant abstracts, and eliminating all variables with poor interrater reliability.

CP occurs in two to four children per 1000 live births. In the US, the prevalence of CP increased from 1.7 to 2.0 per 1000 live births between the mid-1970s and late 1980s,² and was as high as 3.6 per 1000 8-year-old children in 2002.¹ Based on these numbers, approximately 12 000 children with CP are born annually in the US.

In the US, as well as in other developed countries, there is generally more research funding available for conditions that affect adults than children. Even among childhood disorders, funding for CP research lags behind other conditions. For instance, in 2010, an estimated \$21 million of NIH funding went to grants targeting CP, based on the NIH RCDC categorization system. A similar RCDC analysis of NIH funding for cystic fibrosis research in 2010 revealed a total of \$99 million in funding. The annual incidence of CP in the US is about 3 per 1000 births, while

cystic fibrosis occurs in 0.3 per 1000 births. Based on these numbers, the federal government spent \$1750 research dollars on every new case of CP, compared to \$82,500 for every new case of cystic fibrosis in 2010. Similar differences are seen when NIH funding for CP is compared with autism, which received \$218 million of NIH funding in 2010. The annual incidence of autistic spectrum disorder is 11 per 1000 births;⁷ thus, \$4950 NIH research dollars were spent on every new case of autism.

Beyond NIH, private research foundations and patient advocacy groups also play important roles in supporting CP research. However, the amount of funding available outside the NIH for CP research also lags behind support for other childhood disorders. For instance, the Cerebral Palsy International Research Foundation, the only foundation in the US entirely devoted to researching prevention and treatment of CP, had a research budget of \$1.6 million in 2009. In contrast, the US Cystic Fibrosis Foundation and the Juvenile Diabetes Foundation provide about \$85 million and \$156 million annually in research support. Of note, private foundations promoting CP research have typically focused on functional therapies rather than prevention and cure.

Why has there been relatively less funding for CP? The misguided emphasis on labor and delivery complications as the primary cause of CP is one potential reason that there have not been many comprehensive etiological studies. Furthermore, the diagnosis of CP is often confusing to clinicians, researchers, and patients alike. CP is a heterogeneous group of syndromes of motor dysfunction resulting from a wide range of brain disorders,^{8,9} including brain injury of prematurity, global hypoxic-ischemic brain injury, focal arterial and venous infarctions, brain malformations, genetic abnormalities, intrauterine infection, and more. Evidence shows that with the current state of knowledge, we are unable to prevent CP in the vast majority of cases.¹⁰ The underlying causal pathways that lead to each of these types of brain injuries are complex, often intersect, and remain incompletely understood. Several groups have published causal diagrams and roadmaps to CP research, that belie the complexities involved in understanding this heterogeneous disorder.^{11,12}

The term ‘early developmental brain injury/interference’, which focuses on the brain impairment rather than the motor deficits of CP, has been proposed as an alternative framework and approach to CP.¹³ An intended advantage of using this term is to align the CP research community with on-going efforts of the US national BRAIN Initiative (www.nih.gov/science/brain). That is, ‘formally and clearly calling CP a brain condition, rather than highlighting the motoric disturbances, places it where it belongs, next to the robustly supported traumatic brain injury community already in the foreground of the public’s attention’.¹³

Recent efforts to increase public awareness and to boost CP research funding have begun to make positive changes. The work of patient advocacy groups has led to the inclusion of a new statement by the 2015 US Senate

Appropriations Committee: ‘a 5-year strategic plan for cerebral palsy prevention, treatment, and cure through the lifespan with the goal of reducing the number of people impacted by CP overall, as well as improving the opportunity for recovery of those already diagnosed’.¹⁴ Whether there will be adequate funding to support this initiative remains unclear. The Cerebral Palsy Alliance Research Foundation held several research summit meetings which led to the formation of an international multidisciplinary research network called IMPACT for Cerebral Palsy. In 2014, the NIH hosted a State-of-the-Science and Treatment Decisions in Cerebral Palsy Workshop, bringing together leaders in research, patient care, and patient advocacy. This workshop has led to renewed efforts to organize multicenter efforts to further CP research within the US and beyond, and should lead to new opportunities for improving neurological function for children and adults

with CP. Thus, momentum is gaining both in the international and US communities to address the serious gaps in our understanding of the treatment and prevention of CP.

ACKNOWLEDGEMENTS

This study was funded by Paul and Lori Gross, Cerebral Palsy International Research Foundation, CP Daily Living, and Let’s Cure CP. Dr Wu has provided expert witness consultation on medicolegal cases related to CP. Paul Gross, who provided partial funding for this project, also participated in the design of the study, data analysis, and interpretation, and drafting of the final manuscript. The authors would like to thank Cara Long for her assistance with interpreting NIH variables in RePORTER, Emma Anderson for her assistance with calculations of kappa values, and Rebecca Webb for her assistance with creating the figures in the manuscript.

REFERENCES

1. Yeargin-Allsopp M, Van Naarden Braun K, Doernberg NS, Benedict RE, Kirby RS, Durkin MS. Prevalence of cerebral palsy in 8-year-old children in three areas of the United States in 2002: a multisite collaboration. *Pediatrics* 2008; **121**: 547–54.
2. Winter S, Autry A, Boyle C, Yeargin-Allsopp M. Trends in the prevalence of cerebral palsy in a population-based study. *Pediatrics* 2002; **110**: 1220–5.
3. Bax M, Goldstein M, Rosenbaum P, et al. Proposed definition and classification of cerebral palsy, April 2005. *Dev Med Child Neurol* 2005; **47**: 571–6.
4. Centers for Disease Control and Prevention (CDC). Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment—United States, 2003. *MMWR Morb Mortal Wkly Rep* 2004; **53**: 57–9.
5. Advanced NIH Guide Database. Available from: http://grants.nih.gov/grants/guide/search_guide.htm (accessed 9 January 2015).
6. Rubio DM, Schoenbaum EE, Lee LS, et al. Defining translational research: implications for training. *Acad Med* 2010; **85**: 470–5.
7. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators; Centers for Disease Control and Prevention. Prevalence of autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. *MMWR Surveill Summ* 2012; **61**: 1–19.
8. McIntyre S, Blair E, Badawi N, Keogh J, Nelson KB. Antecedents of cerebral palsy and perinatal death in term and late preterm singletons. *Obstet Gynecol* 2013; **122**: 869–77.
9. Wu YW, Croen LA, Shah SJ, Newman TB, Najjar DV. Cerebral palsy in a term population: risk factors and neuroimaging findings. *Pediatrics* 2006; **118**: 690–7.
10. Nelson KB. Can we prevent cerebral palsy? *N Engl J Med* 2003; **349**: 1765–9.
11. IMPACT for Cerebral Palsy. 2011 Summit Report. Available from: <http://impact.cerebralpalsy.org.au/activities/research-summits/2011-summit-report/> (accessed 8 January 2015).
12. ACOG, editor. Neonatal Encephalopathy and Neurologic Outcome. 2nd edn. Washington, DC: American College of Obstetricians and Gynecologists, 2014.
13. Shusterman M. Introducing the term ‘early developmental brain injury/interference’ and a new framework for discussing cerebral palsy. *Dev Med Child Neurol* 2015; **57**: 110–1.
14. Department of Health and Human Services Senate Appropriations Subcommittee. Washington, DC. 2015 (Forthcoming).