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Protocol for a cost–utility analysis of neurostimulation and intensive camp-based therapy for children with perinatal stroke and hemiparesis based on a multicentre clinical trial

Patrick Berrigan [ID],[1] Jacquie Hodge,[2] Adam Kirton,[3,4] Myla E Moretti,[5,6] Wendy J Ungar,[6,7] Jennifer D Zwicker [ID] [1,4,8]

For numbered affiliations see end of article.

Correspondence to
Dr Jennifer D Zwicker;
zwicker1@ucalgary.ca

ABSTRACT

Introduction Perinatal stroke leads to cerebral palsy (CP) and lifelong disability for thousands of Canadian children. Hemiparesis, referring to impaired functionality in one side of the body, is a common complication of perinatal stroke. Standard long-term care for hemiparetic CP focuses on rehabilitation therapies. Early research suggests that patients with hemiparesis may benefit from adjunctive neuromodulation treatments such as transcranial direct current stimulation (tDCS). tDCS uses electric current to stimulate targeted areas of the brain non-invasively, potentially enhancing the effects of motor learning therapies. This protocol describes an economic evaluation to be conducted alongside a randomised controlled trial (RCT) to assess the incremental cost of tDCS added to a camp-based therapy compared with camp-based therapy alone per quality-adjusted life year (QALY) gained in children with hemiparetic CP.

Methods and analysis The Stimulation for Perinatal Stroke Optimising Recovery Trajectories (SPORT) trial is a multicentre RCT evaluating tDCS added to a 2-week camp-based therapy for children aged 6–18 years with perinatal ischaemic stroke and disabling hemiparetic CP affecting the upper limb. Outcomes are assessed at baseline, 1 week, 2 months and 6 months following intervention. Cost and quality of life data are collected at baseline and 6 months and results will be used to conduct a cost–utility analysis (CUA). The evaluation will be conducted from the perspectives of the public healthcare system and society. The CUA will be conducted over a 6-month time horizon.

Ethics and dissemination Ethical approval for the SPORT trial and the associated economic evaluation has been given by the research ethics boards at each of the study sites. The findings of the economic evaluation will be submitted for publication in a peer reviewed academic journal and submitted for presentation at conference.

Trial registration number NCT03216837; Post-results.

Strengths and limitations of this study

► First cost–utility analysis to be conducted for transcranial direct stimulation in paediatric hemiparetic cerebral palsy.

► Resource use data will describe the range of service use where available for the patient population (excluding the first cycle of the camps).

► Sample size was calculated to demonstrate a difference in the primary clinical outcome the Assisting Hand Assessment.

can result in lifelong cognitive and physical impairments, causing substantial impacts to patients and their families.[2] Alongside detrimental impacts to the patients' health, perinatal stroke results in substantial costs to healthcare systems including increased rehabilitation costs as well as broader societal impacts.[3 4]

Standard long-term care for hemiparetic CP focuses on rehabilitation therapies and patient specific symptom management.[5] In addition to standard care, research suggests that children with hemiparesis can benefit from adjunctive treatments such as transcranial direct current stimulation (tDCS).[6 7] tDCS uses electrical current to non-invasively stimulate or inhibit targeted areas of the brain. Research suggests that this type of stimulation can modulate brain plasticity potentially leading to improved motor-function in hemiparesis patients.[8]

Economic evaluation can help guide policymaking and resource allocation decisions. Clinical research on the efficacy of tDCS is promising, however based on the findings of a recent systematic review, there has been no evaluations of the value for money of tDCS within the paediatric hemiparesis population

INTRODUCTION

Cerebral palsy (CP) is a leading cause of childhood physical disability.[1] Hemiparetic CP due to perinatal stroke is a common subtype and

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to date.[9] Most commonly, value for money of healthcare interventions is assessed using cost-effectiveness analysis (CEA). CEA combines cost and a single measure of effectiveness into a metric referred to as an incremental cost-effectiveness ratio (ICER).[10] An ICER is calculated by dividing the difference in cost by the difference in effectiveness between two interventions. When the effectiveness outcome included in a CEA is a universal preference-based measure of generic health-related quality of life (HRQoL), known as a utility measure, the analysis is referred to as a cost–utility analysis (CUA). This is the analytical approach recommended by many funding agencies.[10–12]

This protocol describes a CUA to be conducted alongside a randomised controlled trial to assess the incremental cost of tDCS added to a camp-based therapy compared with camp-based therapy alone per QALY gained in children with hemiparetic CP. A secondary CEA will be undertaken using the study's primary clinical effectiveness measure the Assisting Hand Assessment (AHA).[13] The AHA is a tool to evaluate hand function in children with unilateral upper limb deficits. This evaluation will be performed alongside the Stimulation for Perinatal Stroke Optimising Recovery Trajectories (SPORT) trial. The SPORT trial has sites in Calgary, Edmonton, and Toronto and provides camps once per year during the summer months. The SPORT trial plans to continue for four cycles (summer 2017 to summer 2021) with data collection targeted for completion by spring 2022. Of note, no camps were held in summer 2020 due to COVID-19.

At present, the value for money of tDCS relative to standard care has not been assessed. This paucity of information will inhibit the ability of public and private funders to make reimbursement decisions regarding the adoption of tDCS into the clinical setting. The findings of the present study will provide policy-makers with information to inform such decisions.

METHODS AND ANALYSIS
Recruitment
Participants are recruited for the SPORT trial through established programmes by the clinical research team. In Calgary and Edmonton, participants are recruited from the Alberta Perinatal Stroke Project, a population-based cohort of more than 1000 MRI-confirmed perinatal stroke patients.[14] In Toronto, participants are recruited from CP research cohorts at Holland Bloorview Kids Rehabilitation Hospital. All participants in the SPORT trial are eligible for the economic evaluation.

Inclusion criteria
Inclusion criteria are clinical and MRI-confirmed perinatal ischaemic stroke, symptomatic hemiparetic CP that includes a child/parent perceived deficit and informed consent. Exclusion criteria included other neurological disorder not related to perinatal stroke, multifocal stroke, severe hemiparesis (Manual Ability Classification System

V),[15] severe spasticity (Modified Ashworth Scale >3),[16] severe delay or inability to comply with protocol, unstable epilepsy, any transcranial magnetic stimulation or MRI contraindication and orthopaedic surgery, constraint, brain stimulation or other modulatory therapy in past 6 months or botox in the past 4 months.

Sample size calculation
Sample size for the SPORT trial was calculated based on that needed to detect a five unit difference in the SPORT trial's primary clinical outcome (AHA) at an alpha=0.05 and a power of 0.90.[13] This calculation indicated that the clinical trial would need to recruit a sample of 80 participants (40/group).

Randomisation and blinding
A permuted block randomisation approach was used to allocate participants to groups by study site. Approximately 50% of participants will receive their therapy at Calgary and approximately 25% will receive therapy in Edmonton and Toronto, respectively. Participants and evaluators will be blinded to their study group (treatment vs control) with participants in the control group receiving sham tDCS.

Intervention
Participants are randomised to control and experimental treatment groups. Each group receives the same intensive motor therapy based on individually set goals, constrained-induced movement therapy (CIMT) during the first week and bimanual therapy during the second. CIMT, promotes functional use of the affected limb by restricting the use of the less-affected limb. This increased use encourages plasticity, which can improve motor function.[17 18] Participants in the experimental group receive daily tDCS sessions while participants in the control group receive a sham session of tDCS. Camps will run for 10 days (75 hours) and use the following structure: 2 hours/day working 1:1 with a dedicated occupational therapist; 1.5 hours/day independent gross motor function work; 1.5 hours/day group motor function work; 1 hour/day lunch; 0.5 hours x 2/day social snack; and 0.5 hours/day fun breaks. On completion of camp, participants in both groups receive a structured home-based programme to complete over the course of 6 months focusing on the same principles as those worked on in camps.

Perspective
Based on the recommendation of the Canadian Agency for Drugs and Technologies in Health (CADTH), the national authority on economic evaluation in the study jurisdiction, the perspective of the public healthcare payer will be used for the reference case analysis.[10] For paediatric economic evaluation, a societal perspective is also recommended to capture parent/caregiver productivity costs in addition to healthcare, educational, and families' out-of-pocket costs.[11 19]

Time horizon

In the SPORT trial, data collection will occur at baseline, 1 week, 2 months and 6 months. Results of the reference case CUA and secondary CEA with AHA will be calculated with a 6-month time horizon.

Health outcomes for economic evaluation

Generic HRQoL will be measured using the Health Utilities Index (HUI). Briefly, the HUI measures the impact of health on abilities, activities, and emotions. Utility scores are a value typically bounded between zero and one that reflects a person's health as a percentage of perfect health. QALYs are calculated by aggregating utility scores over a period of interest. To calculate QALYs, utility scores will be derived from data collected using the HUI3.[20] The HUI3 Multi-Attribute Utility Function will be applied to HUI3 data to derive utility weights (http://www.healthutilities.com/). QALYs over the time horizon will be calculated for each patient based on the area under the curve formed by participants' quality of life trajectory over time (0–6 months). Mean QALYs per patient will be determined for each group. HUI3 data will be collected for all four camp cycles using a parent/caregiver proxy version of the questionnaire.

In the CEA, the difference between groups in AHA scores at 6 months will be used to measure effectiveness. The AHA is a validated and reliable assessment tool to measure bimanual function in children with hemiparetic CP.[13] The AHA is scored using a 4-point ordinal scale and will be collected at 0, 2 and 6 months for all four cycles.[13] The AHA will be administered by trained therapists.

Resource use and costing

Costing of direct health and non-health costs, direct patient costs and indirect (productivity) costs will be conducted by multiplying volume of resource use by a unit price for each item. The child will be the unit of analysis for the present study and utilisation incurred by the healthcare system, patient, or caregivers will be assigned to the child for analysis.

Item identification

Volumes of resource use and out-of-pocket costs for items related to (1) school programmes; (2) occupational therapy or physiotherapy; (3) child-focused recreation activities; (4) additional services related to the child's condition; (5) purchased materials and equipment and (6) caregiver time associated with treatment and care are collected using the Resource Use Questionnaire (RUQ), a tool validated for use in participants with neurodevelopmental disabilities.[21 22] Government tax deductions, subsidies, and other financial supports received by families are also collected.

Measurement

The RUQ was added to the set of data collection tools included in the SPORT trial after commencement of the trial to enable a CUA. As a result, RUQ data were not collected in the first year of the SPORT trial. The RUQ is administered at baseline and 6 months for the final three camp cycles. The RUQ used in the SPORT trial has a 3-month recall period meaning that parents are asked to report their child's use of resources for the 3 months prior to the interview in which the RUQ is administered. The 3-month resource use identified via the RUQ at baseline and follow-up will be used to extrapolate resource use for the 6-month duration of the trial. The total cost per patient per month will be calculated and this will be used in extrapolation.

Valuation

Participants in both the control and treatment groups will receive the same care with the exception of the treatment group receiving active tDCS and control group receiving sham sessions. For SHAM sessions, patients will be placed in the tDCS and a pre-existing setting available on the device will be used that simulates a session of tDCS without administering the treatment. The cost of sham sessions in the control group will be excluded as protocol-driven costs. For the healthcare system perspective, costs will include: (1) tDCS sessions; (2) occupational therapy or physiotherapy; (3) child-focused recreation activities and (4) additional services related to the child's care paid for by the public healthcare system. For the societal perspective, costs will include (1) each of the cost categories 1–4 mentioned above; (2) educational cost related to the child's condition; (3) parent lost productivity and (4) parent out-of-pocket costs.

Intervention cost

The cost of tDCS will be estimated from: (1) the compensation to technicians operating the tDCS including training costs; (2) the price of the tDCS device amortised over its expected useful lifespan; (3) any maintenance or licensing fees associated with the device and (4) the cost of materials and supplies associated with using the device such as disposables. Sources for these prices will be provided by the clinical research team. Fixed costs (the price of the tDCS device and maintenance or licensing fees associated with the tDCS device) will be aggregated and divided by the estimated number of uses over the machine's lifespan. Estimates for the number of uses will be based on information provided by the clinical research team and the manufacturer. Estimates for the variable costs (the compensation to technicians operating the tDCS and the cost of materials and supplies associated with using the device) will be made for a standard tDCS session using the guidance of the clinical team. Technician compensation for a session will reflect wage rate multiplied by the time a session requires. The fixed and variable cost associate with a use of tDCS will be aggregated to form an estimate of the total cost per use. The total cost per use will be multiplied by the number of sessions each child received, which will then be averaged over the tDCS group to obtain an estimate of the cost of tDCS sessions per patient.

To estimate the cost of the camp therapy programme, the present study will include: the wages of providers delivering treatment (eg, physical therapists); the cost of materials and supplies associated with the programme; and the cost of licenses and other fees associated with running the camp. Sources for these prices will include publicly available collective bargaining agreements and the clinical research team. These costs will be aggregated to estimate a total cost for the camp and divided by the number of attendees to obtain an estimate of the cost of camp per patient. We assume that the ratio of patients to attendees is fixed. Subsequently, scaling up would require additional staff. Travel costs, the cost of hospital space, and costs related to accommodations for families who require lodging to attend camps will not be considered in the analysis.

Direct healthcare and educational cost

Alberta, Canada will be used as the reference jurisdiction for estimating unit prices. Estimates of the unit price for each reported resource will be multiplied by the volume of utilisation for that resource. For fee-for-service providers (eg, physicians) the fee corresponding to the reported service will be applied.[23] For salaried employees (teachers, social workers, nurses, etc) the time taken for a typical session reported by parents and recorded in the RUQ will be multiplied by the wage rate of the provider performing the task.[24] Overhead cost and relevant employer contributions (pension and other benefits) will be applied when available. If a professional service is reported for which an appropriate wage cannot be determined from available collective bargaining agreements, the mean professional hourly wage for the service will be multiplied by the time required to deliver the reported service.[25] Direct health and educational costs will be summed for each patient individually, to obtain each patients' total cost related to direct health and education care over the follow-up period.

Caregiver lost productivity costs and family out of pocket costs

For analysis using the societal perspective, lost caregiver productivity will be monetised using a human capital approach.[10] For missed time at work or from usual daily activities by caregivers due to caring for a child with CP, the average hourly wage in the corresponding jurisdiction obtained from Statistics Canada[26] will be multiplied by hours lost. The out-of-pocket costs of child-focused recreation activities, additional services, purchased materials and equipment will be obtained from parent reports on the RUQ. Lost productivity and out of pocket costs will be summed for each patient individually, to obtain each patients' total lost productivity and out of pocket costs over the follow-up period.

All items will be costed using 2021 Canadian dollars (the final year of the trial). Where necessary (eg, out-of-pocket costs reported in earlier years) will be adjusted for inflation using the Canadian consumer price index for health care to reflect this year.[27] Costs for each category (cost per patient of tDCS sessions, cost per patient of camp, direct health and educational costs and caregiver lost productivity and out of pocket costs) will be aggregated at the patient level for both the public healthcare system and societal perspectives to obtain the total cost per patient for each patient. A cost-item table listing items, source for volume and source of unit price will be provided that is organised by category and perspective.

Data analysis

For the reference case analysis, the mean QALYs for each group will be compared over the 6-month trial using patient level regression. To assess the difference in QALY between groups we will use ordinary least squares (OLS) and control for a set of covariates including study site, age, baseline HUI3 scores, and severity of disability. For the reference case analysis, the mean cost per patient for each group over the 6-month trial will also be compared using patient level regression. To assess the difference in cost between groups we will use OLS and control for the set of covariates including study site, age, baseline cost and severity of disability. If the fitted model violates the OLS normality assumption than a log transformation will be applied. Back transformation will be performed using the smearing estimator approach to produce a difference in cost to inform the ICER.[28] For all regression analyses, we will report the mean difference between groups, the variance and p value associated with the mean difference, and the goodness of fit for the corresponding regression model using R-squared.

Reference case CUA

In the reference case analysis, the ratio of the difference in mean cost between groups to the difference in mean QALYs per group will be used to estimate an ICER from the publicly funded healthcare payer and societal perspectives if one of the interventions is associated with higher cost and better effectiveness. A bootstrapped analysis will be conducted for the CUA. Specifically, the study will use the between group difference in cost and QALYs, tDCS vs control, to parameterise distributions for both the difference in cost and QALYs. Values from each distribution will be drawn and then used to calculate ICER. This process will be repeated 5000 times and the results presented on a cost-effectiveness acceptable curve (CEAC). A CEAC is a graphical display that demonstrates the probability than an intervention is cost-effective relative to another intervention across a range of threshold willingness-to-pay values. The 5000 draws was selected, as it is the minimum number of draws recommended by CADTH for economic evaluations of health technologies.

Secondary CEA

In the CEA, the ratio of the difference in mean cost between groups to the difference in AHA scores between groups will be used to estimate an ICER from the publicly funded healthcare payer and societal perspectives if one

of the interventions is associated with higher cost and better effectiveness.

Sensitivity analysis

We will undertake sensitivity analysis to assess the robustness of the reference case findings. These analyses will be undertaken to test variations in assumptions regarding uncertain estimates related to resource use volume and price. Variables for which uncertainty will be investigated include provider wages and compensations, prices/costs related to operating camps, and price per use of the tDCS device. Of note, there is a downward trend regarding the unit price of the tDCS device. As a result, we will assess scenarios where tDCS has lower cost than is used in the primary analysis. Finally, we will conduct a one-way sensitivity analysis in which key parameters will be varied over relevant intervals to assess the sensitivity of the ICER to changes in the value of the included parameters (ie, physician fees, price per use of tDCS device, etc).

Missing data

The extent of missing data and missing cases will be identified. If there are missing data, the data will be examined to determine the nature of the missing data (ie, missing completely at random, missing at random, etc).[29] Several approaches will be considered to deal with missing data: (1) analysis of complete cases only (2) not including variables with high extent of missing data and (3) imputing missing values. For the latter approach, standard multiple imputation methods will be used, where multiple complete datasets will be created, parameters of interest will be estimated in each complete dataset and pooled parameter estimates across the datasets will be calculated.[30 31] The R package mice will be used to impute missing data.[32]

Discount rate

Since all costs and outcomes occur within 1 year, a discount rate will not be applied.[10]

Patient and public involvement

The SPORT trial is a project within the CHILD-BRIGHT network. CHILD-BRIGHT is a national network that focuses on research for children and families with neurodevelopmental disorders and has an advisory committee made up of participants and families that help to shape CHILD-BRIGHT's research. Furthermore, the goal oriented tasks portion of the camp allows children to set their own goals and works with children to achieve these.

Data management

Clinical trial data will be saved and password protected at CHILD-BRIGHT's data coordinating centre (DCC) on a secure server at the Women & Children's Health Research Institute at the University of Alberta (Edmonton, Alberta, Canada) to which DCC employees and study research staff will have access. Administrators at the DCC will transfer deidentified (personal identifiers removed) trial data to the economic evaluation team for analysis on completion of the trial. For economic analysis, participants will be identified by the study ID given by the clinical research team. From the transferred data, an economic dataset will be constructed by adding costs and prices to utilisation data collected during the trial (described above). All data received and created by the health economics team will be stored on an encrypted and password protected cloud based storage platform with servers located in Canada.

ETHICS AND DISSEMINATION

All study participants have provided informed consent to participate in the SPORT trial. Ethical approval for the SPORT trial and the associated economic evaluation has been given by the respective Research Ethics Board (REB) for each of the study sites (University of Calgary's Consolidated Health Research Ethics, Holland Bloorview REB, and the University of Alberta Health REB). The study findings will be submitted for publication in a peer-reviewed journal and presentation at a scientific conference. The findings will also be made available to funding and policy decision-makers within the jurisdictions of the study sites. The authors will also use CHILD-BRIGHT's knowledge translation team to further spread findings.

DISCUSSION

To inform the implementation and uptake of interventions in clinical practice, guidelines recommend providing evidence of value for money.[10 33] A recent systematic review highlights studies that have assessed cost-effectiveness in CP and describes a number of gaps in the current economic research.[9] To our knowledge, no study has assessed the cost-effectiveness of tDCS in paediatric hemiparesis. To improve transparency, this manuscript describes the first within-trial economic evaluation designed to assess the cost-effectives of tDCS in children with perinatal stroke and hemiparetic CP. A benefit of conducting an economic evaluation of clinical trial data versus using a theoretical decision model is that real world stochastic data can be used to generate findings and fewer assumptions are required. Furthermore, given the paucity of data in this population at present, there is limited information to inform a model for the use of tDCS in paediatric hemiparesis. A drawback of this approach is that costs and outcomes will reflect a relatively short time horizon. As at present the value for money of tDCS relative to standard care has not been assessed, this paucity of information will inhibit the ability of public and private funders to make reimbursement decisions regarding the adoption of tDCS into the clinical setting. The findings of the present study, will provide decision-makers with information to inform such decisions.

Author affiliations
[1]School of Public Policy, University of Calgary, Calgary, Alberta, Canada
[2]Calgary Pediatric Stroke Program, Alberta Children's Hospital, Calgary, Alberta, Canada
[3]Departments of Pediatrics and Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

⁴Alberta Children's Hospital Research Institute, University of Calgary, Calgary, Alberta, Canada
⁵Ontario Child Health Support Unit and the Clinical Trials Unit, Hospital for Sick Children, Toronto, Ontario, Canada
⁶Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada
⁷Technology Assessment at SickKids, Program of Child Heath Evaluative Sciences, Hospital for Sick Children, Toronto, Ontario, Canada
⁸Faculty of Kinesiology, University of Calgary, Calgary, Alberta, Canada

Contributors PB: developed manuscript; JH: contributed clinical expertise and assisted with manuscript development; AK: contributed clinical expertise and assisted with manuscript development; MEM: contributed health economic expertise and assisted with manuscript development; WU: contributed health economic expertise and assisted with manuscript development; JZ: contributed health economic expertise and assisted with manuscript development.

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ORCID iDs
Patrick Berrigan http://orcid.org/0000-0002-3750-7978
Jennifer D Zwicker http://orcid.org/0000-0002-0722-5929

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