Evidence-based Practice Center Systematic Review Protocol

Project Title: *Can Physical Activity Improve the Health of Wheelchair Users? A Systematic Review*

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(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

Approximately 65 million people worldwide require the enhanced mobility of wheelchairs.[1] The U.S. Department of Health and Human Services indicates that routine physical activity programs combining aerobic exercise with muscle strength and balance training improves fitness, function, and quality of life for individuals with physical disabilities.[2]

The populations of interest for this systematic review are those with multiple sclerosis (MS), cerebral palsy (CP), and spinal cord injury (SCI), as these populations provide a diversity of wheelchair users and potential users. SCI, MS, and CP have very different physiologic mechanisms (brain vs. spinal cord, degenerative vs. not) and demographic profiles (male vs. female predominance, childhood vs. adult onset). While there are differences between these populations, there are common hurdles that most wheelchair users must overcome, including psychological and physical barriers as well as those related to access to healthcare and appropriate physical activity programs. With regard to barriers to healthcare, one study found many wheelchair SCI patients often did not receive age-appropriate preventive care such as colonoscopy or mammography.[3] Preventive care also includes maintaining a healthy weight or body composition and maintaining physical fitness. Unfortunately, individuals with limited mobility are at greater risk for obesity or increased body fat,[4-6] diabetes,[7-9] and dyslipidemia[10,11] (among other chronic conditions), putting them at increased risk for cardiovascular events such as myocardial infarction,[11,12] stroke,[9,12,13] and death.[12,14] Increased risk for morbidity and mortality may be due, in part, to the specific disease that limits mobility or leads to the use of a wheelchair, the treatment for the disease (e.g., steroids used to treat MS), and/or a sedentary lifestyle. The National Academies of Sciences, Engineering, and Medicine's 2017 report on the use of assistive technologies to enhance activity recommends that individuals who require wheeled and seated mobility devices receive regular evaluations of their physical condition.[15] Evaluation should include at least annual assessments of the functioning and fitting of the devices, ergonomics and safety, ability to use the device, underlying disorder and secondary health conditions, functional needs, and the individual's satisfaction. Access to appropriate care can facilitate education, linkage to activity resources, and encouragement of physical activity to help mitigate these risks.

People with disabilities also face a number of barriers to exercise. Skill at using a wheelchair, fatigue, pain, heat sensitivity, and self-efficacy have been proposed as barriers to physical activity in those with MS.[16-19] Individuals who only sometimes need a wheelchair may not be comfortable with their wheelchair skills and therefore may not participate in wheelchair sports or physical activities.[20] A review of Canadian community-based physical activity and wheelchair mobility programs points out a clear need for more programs, particularly those that assess long-term impact.[21] Longer time since injury is associated with lower fitness levels in SCI with paraplegia.[15] Decreased strength and muscle mass associated with aging increases risk for shoulder injury, and elderly wheelchair users need specific interventions to preserve mobility.[22]

Physical activity has been shown to improve body composition,[23-25] glucose metabolism,[25-27] and lipid profiles,[25,28] and to decrease risk of morbidity and mortality in nondisabled people.[24,29] Physical activity could similarly benefit those with disabilities. Recently published SCI guidelines recommend moderate to vigorous intensity aerobic exercise at least two times per week and strength exercise for each major functioning muscle group twice per week.[30] Verschuren et al. recommend aerobic sessions and strength training two times per week for individuals with CP,[31] while Halabchi et al. recommend aerobic exercises, strength training, and daily flexibility and stretching exercises for individuals with MS.[32] In the past, exercise was not recommended for individuals with MS due to fear of worsening of symptoms;[33] however, more recent evidence suggests that physical activity improves health outcomes in people with MS, CP, and SCI. The updated 2018 Physical Activity Guidelines for Americans now recommend between 2.5 to 5 hours of moderate aerobic exercise weekly, or over 1 hour to 2.5 hours of vigorous aerobic exercise weekly, plus muscle strengthening actives for people with physical disabilities.[2]

This systematic review will summarize and synthesize current research on the benefits and harms of physical activity for wheelchair users and potential wheelchair users. This topic was nominated by the Director of the National Center for Medical Rehabilitation Research for a Pathways to Prevention (P2P) workshop to assess the benefits and harms of physical activity on the physical and mental health of adults, children, and adolescents using, or at risk for using, wheeled mobility devices, such as wheelchairs or scooters. The populations of interest are those with MS, CP, and SCI. High priority outcomes are cardiovascular mortality; myocardial infarction; stroke; pulmonary function tests; VO_2 max; development of diabetes; hemoglobin A1c (HbA1c); bowel, bladder, and sexual function; decubitus ulcers; development of obesity; body mass index (BMI); weight; depression; quality of life; time to wheelchair use; amount of wheelchair use; falls; function; autonomic dysreflexia; and spasticity. We will also evaluate additional outcomes, physical activity interventions, inclusion/exclusion criteria, and research methodologies to identify research gaps and future research needs. The outcomes of pain and cognition are not included because it is expected that the magnitude of the literature involved would indicate that these topics should be their own reviews.

Our review will be used by National Institutes of Health (NIH) Office of Disease Prevention (ODP) Working Group to inform a P2P workshop to determine the effects of activity interventions, health consequences, and benefits and harms of physical activity, as well as future research needs in patients with MS, CP, and SCI. The objective is to understand the benefits and harms of physical activity for people currently using or at risk

for using a wheeled mobility device and to identify gaps for future research focus—ultimately improving patient lives and providing potential healthcare cost savings.

II. The Key Questions

Key Question 1: What is the evidence base on physical activity interventions to prevent obesity, diabetes, and cardiovascular conditions, including evidence on harms of the interventions in people with MS, CP, or SCI who are at risk for or currently using a wheeled mobility device?

a. What interventions have been studied?
b. What outcomes have been studied?
c. What inclusion/exclusion criteria have been used in studies?
d. What other research methodologies (control/comparison group design, length of intervention, research setting) have been used?

Key Question 2: What are the benefits and harms of physical activity interventions for people with MS, CP or SCI who are at risk for or currently using a wheeled mobility device?

a. Does physical activity improve clinical outcomes such as cardiovascular disease, diabetes, overweight or obesity, mental health, or sexual function?
b. Does physical activity improve intermediate outcomes such as physical fitness, obesity, or bone density?
c. Does physical activity reduce the harms of immobility, such as incidence of decubitus ulcer, urinary tract infection, bowel dysfunction, or autonomic dysfunction?
d. Does physical activity decrease the risk for adverse outcomes of disorders associated with wheeled mobility device use, such as spasticity, autonomic dysreflexia, or muscle contractures?
e. What are the harms of physical activity, such as injuries that are associated with wheeled mobility device use (e.g., falls, tips, overuse injuries)?
f. Do the benefits or harms of physical activity vary by the location of the intervention (e.g., home, community, clinic), amount of training or instruction (e.g., no training, some training, all physical activity sessions with training), or by the level of supervision (e.g., inpatient, telehealth)?

Key Question 3: What are the patient factors that may affect the benefits and harms of physical activity in patients with MS, CP or SCI who are at risk for or currently using a wheeled mobility device?

a. Do the benefits and harms of physical activity vary by age, sex, or race/ethnicity?
b. Do the benefits and harms of physical activity vary by primary disease or injury that led to wheelchair use?

Key Question 4: What are methodological weaknesses or gaps that exist in the evidence to determine benefits and harms of physical activity in patients with MS, CP or SCI who are at risk for or currently using a wheeled mobility device?

a. What types of studies supported conclusions in Key Questions 2 and 3?

b. What are the major weaknesses in study designs?
c. What would improve ability of future research to address the Key Questions?

Population(s):

- *Include for KQ1, KQ2, and KQ3:* Patients using or at risk for using wheeled mobility devices (i.e., patients with MS, CP, or SCI); in studies of mixed populations, at least 80 percent will be individuals with MS, CP, and/or SCI.
- *Exclude:* Other populations.

Interventions:

- *Include for all KQs:* Any gross motor intervention with a defined period of directed physical activity that is expected to increase energy expenditure. Intervention must have a minimum of 10 sessions on 10 different days of activity in a supervised individual or group setting. Include: aerobic exercise, strength training, standing, balance, flexibility, and combination interventions. (See Table 1 for a list of suggested physical activities.)
- *Exclude:* Unobserved, self-directed, or recalled physical activity; parent or caregiver observed interventions; interventions that do not target the whole body (e.g., interventions to improve reaching or to improve the function of one joint, partial body vibration).

Comparators:

- *Include for all KQs:* Comparisons to no physical activity or other types of physical activity or a behavioral intervention with a physical activity outcome.
- *Exclude:* Comparisons to other active comparators such as drug therapy.

Outcomes:

- For KQ1: Outcome measures, physical activity interventions, inclusion/exclusion criteria, and research methodologies related to prevention of obesity, diabetes, cardiovascular conditions, or harms; types of studies or bodies of studies supporting conclusions for KQs 2 and 3.
- For KQ2 and KQ3: Benefits and harms of physical activity including: (a) clinical outcomes such as cardiovascular mortality, myocardial infarction, stroke, diabetes, mental health, obesity/overweight, and sexual function; (b) intermediate outcomes such as physical fitness, HbA1c, bone density, and resting heart rate; and (c) subgroup differences based on location of intervention (e.g., home, community, clinic), level of instruction or training (e.g., no training, some training, all physical activity sessions with training), and level of supervision (e.g., inpatient, telehealth).
- For KQ4: Major weakness in study design, items that improve the ability to address the KQs. (See Table 2 for list of outcomes).
- *Exclude:* Outcomes not used to make clinical decisions (e.g., estradiol level, muscle thickness).

Timing:

- *Include for all KQs:* At least 10 days with at least one session of physical activity each day.
- *Exclude:* Acute spinal cord trauma stabilization period, immediate postoperative period (e.g., after surgeries to improve musculoskeletal function in CP).

Settings:

- *Include for all KQs:* Any U.S. or U.S.-applicable study, including clinic, home (provided physical activity is observed by healthcare or research staff), or community setting (e.g., gym or athletic class).
- *Exclude:* Non-U.S.-applicable setting.

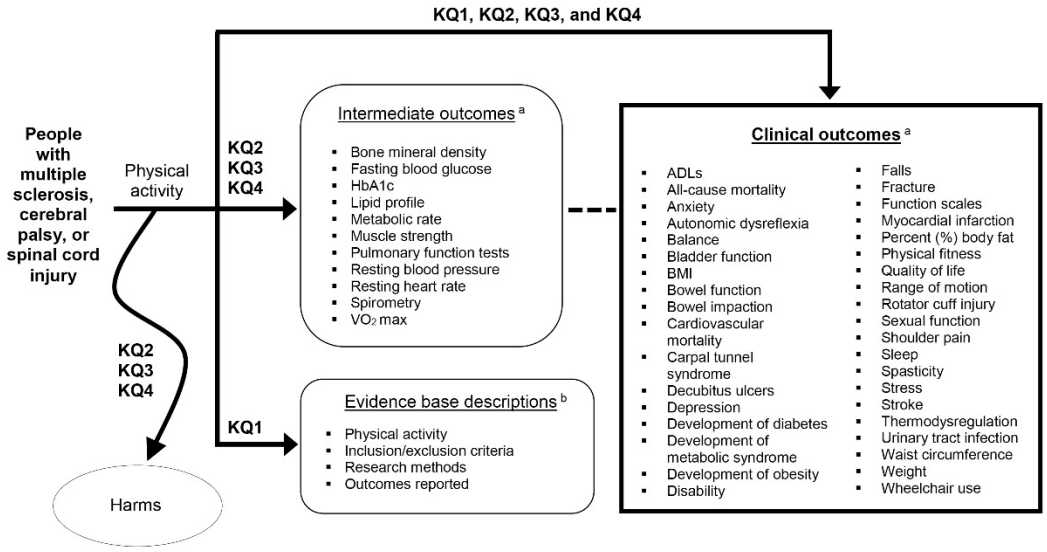
Study design:

- *Include for all KQs:* Clinical trials and observational studies (cohort studies and case-control studies).
- *Include for all KQs:* Studies with the following minimum sample sizes: MS (n=30), CP (n=20), SCI (n=30).
- *Include for all KQs:* Studies published since 2008; systematic reviews published since 2014.
- *Include, if needed, due to lack of clinical trials or controlled observational studies:* Pre-post studies.
- *Exclude:* Case report and case series.

III. Analytic Framework

The analytic framework illustrating the populations, interventions, outcomes, as well as the adverse effects and harms that will direct the literature search and synthesis is in Figure 1.

Figure 1. Analytic framework for physical activity and health in wheelchair users



Abbreviations: ADL=activities of daily living, BMI=body mass index, KQ=Key Question
[a] Outcomes are specified in Table 2
[b] Studies that are evaluating prevention of obesity, diabetes, cardiovascular conditions, and harms

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

The criteria for inclusion and exclusion of studies are designed to identify findings that can answer the Key Questions and are based on the population, intervention, comparators, outcomes, timing, setting, and study design, as shown in Table 1.

The Evidence-based Practice Center (EPC) adjusted and reordered the initial Key Questions and Population(s), Interventions, Comparisons, Outcomes, Timing, Setting (PICOTS) proposed by the NIH P2P Working Group. The population for this review is people using or at risk for using wheeled mobility devices due to MS, CP, or SCI. Limiting the population to these three groups was agreed upon as a method of capturing a broad, diverse population of wheelchair users and potential wheelchair users. Sample size, clarification of specific interventions and outcomes for inclusion or exclusion, and the possibility of grouping outcome measures getting at the same construct when rating strength of evidence (e.g., doing strength of evidence for depression overall rather than

for each depression scale), and prioritization of outcomes to review for strength of evidence ratings were discussed and agreement reached. Study sample sizes will be ≥30 for MS and SCI, and ≥20 for CP. Study designs indicated in Table 1 will be included. Pre-post studies that otherwise meet inclusion criteria will be considered for inclusion in the absence of higher quality evidence.

Prioritized outcomes for which we will assess the strength of evidence include: cardiovascular mortality; myocardial infarction; stroke; pulmonary function tests; VO_2 max; development of diabetes; HbA1c; bowel, bladder, and sexual function; decubitus ulcers; development of obesity; BMI; weight; depression; quality of life; time to wheelchair use; amount of wheelchair use; falls; function; autonomic dysreflexia; and spasticity (Table 2).

Given the current 2008 guidelines, and the large number of potentially relevant publications, studies published since 2008 and systematic reviews published since 2014 will be included. Studies published earlier than these dates will be excluded. We do not anticipate that any systematic review will include only studies that meet our inclusion criteria, so we plan to use systematic reviews only to identify additional studies.

These decisions regarding study design, study size, publication date range, and prioritization of outcomes were developed in collaboration with the NIH P2P Working Group and reviewed with a panel of technical experts.

Table 1. PICOTS—Inclusion and exclusion criteria

PICOTS	Inclusion	Exclusion
Population	Patients using or at risk for using wheeled mobility devices due to MS, CP, or SPI.	• Other populations • Studies of mixed populations with <80% MS, CP, SCI
Intervention	Any gross motor intervention with a defined period of directed physical activity that is expected to increase energy expenditure. Intervention must have a minimum of 10 sessions of activity on 10 days or more in a supervised or group setting. Include aerobic exercise, strength training, standing, balance, flexibility, and combination interventions. *Included activities (not exhaustive, additional activities may qualify):* **Standing/positional** • Standing frame • Whole body vibration **Balance flexibility** • Stretching/flexibility • Martial arts (e.g., Tai Chi) • Yoga or Pilates • Hippotherapy (equine-assisted therapy) **Strength/resistance training** • Resistance bands • Weight lifting **Physical/aerobic Exercise** • Arm ergometry • Robot-assisted gait training • Cycling (stationary, recumbent, or arm) • Swimming • Weight lifting/strength training • Aquatherapy • Group exercise • Functional electronic stimulation • Team sports • Treadmill (including with body weight support)	• Interventions with <10 sessions • Interventions over a period lasting <10 days • Unobserved physical activity • Family- or caregiver-observed physical activity • Patient-recalled physical activity • Postoperative physical activity • Intervention focused on improving reaching • Interventions without whole body effect (e.g., targeting one joint)

PICOTS	Inclusion	Exclusion
Comparator	Comparisons to no physical activity or other types of physical activity or behavioral counseling.	• All other active controls
Outcomes	**Cardiovascular** • Cardiovascular mortality, myocardial infarction, stroke, all-cause mortality, resting heart rate, resting blood pressure, lipid profile **Respiratory** • Pulmonary function tests, VO_2 max/peak, spirometry **Endocrine** • Development of diabetes, HbA1c, fasting blood glucose, development of metabolic syndrome, metabolic rate **Gastrointestinal** • Bowel function, bowel impaction **Genitourinary** • Bladder function, urinary tract infection **Musculoskeletal** • Fracture, bone mineral density, muscle strength, rotator cuff injury, shoulder pain, range of motion **Reproductive** • Sexual function **Integumentary** • Decubitus ulcers **Body composition** • Weight, BMI, development of obesity, waist circumference, % body fat **Mental health** • Depression, quality of life, anxiety, stress, sleep **General function** • Falls, wheelchair use, function scales, disability, ADLs, balance, physical fitness **Neurological** • Autonomic dysreflexia, spasticity, thermodysregulation, carpal tunnel syndrome	• Outcomes not used to make clinical decisions (e.g., estradiol) • Other outcomes (e.g., head pitch and roll, kinematic variables, stepping kinematics, reaching, muscle thickness, muscle quality, blood flow restriction, premotoneuronal control) • Hospitalization or length of stay • Cognition • Pain other than shoulder pain
Timing	At least 10 days with at least one session of physical activity per day.	• Acute SCI, undergoing stabilization • Immediate post-operative period
Setting	Any setting, including, clinic, home, or community setting (e.g. gym or athletic class). Physical activity occurring in the home must still be observed by medical, research, or athletic staff.	• Non-U.S. applicable studies (See Appendix B, Table B-1)
Study designs	• Randomized controlled trials published since 2008 • Controlled observational studies published since 2008 • Systematic reviews published since 2014 for pearling of studies • Potentially include pre-post studies in the absence of clinical trials and controlled observational studies • Studies with the following sample sizes: MS (n≥30), CP (n≥20), SCI (n≥30).	• All other study designs (e.g., case series and case reports) • Studies published prior to 2009 • Systematic reviews published prior to 2015

Abbreviations: ADL=activities of daily living, AP=anterior tilt position, BMI=body mass index, CP=cerebral palsy, HbA1c=hemoglogin A1c, MS=multiple sclerosis, SCI=spinal cord injury

Table 2. Outcomes

System	Prioritized Outcomes	Other Outcomes
Cardiovascular	Cardiovascular mortality Myocardial infarction Stroke	• All-cause mortality • Lipid profile • Resting blood pressure • Resting heart rate
Respiratory	Pulmonary function tests VO_2 max/peak	• Spirometry
Endocrine	Development of diabetes HbA1c	• Development of metabolic syndrome • Fasting blood glucose • Metabolic rate
Gastrointestinal	Bowel function	• Impaction
Genitourinary	Bladder function	• Urinary tract infection
Musculoskeletal	*None prioritized*	• Bone mineral density • Fracture • Muscle strength • Range of motion • Rotator cuff injury • Shoulder pain
Reproductive	Sexual function	*None*
Integumentary	Decubitus ulcers	*None*
Body Composition	Body mass index Development of obesity Weight	• Percent (%) body fat • Waist circumference
Mental Health	Depression Quality of life	• Anxiety • Sleep • Stress
General Function	Falls Function scales Wheelchair use	• Activities of daily living • Balance • Disability • Physical fitness
Neurological	Autonomic dysreflexia Spasticity	• Carpal tunnel syndrome • Thermodysregulation

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Publication Date Range: We will limit the search to studies published since 2008 and systematic reviews since 2014. An updated literature search for new publications will be conducted while the draft report is posted for peer review and public comments.

Literature Databases: MEDLINE®, CINAHL®, PsycINFO®, Cochrane CENTRAL, Embase®, and Rehabilitation and Sports Medicine Source will be searched. ClinicalTrials.gov will also be searched to capture gray literature. These databases are broad enough to capture the study types, the populations (MS, CP, and SCI), and physical activities to be reviewed. The full search strategies are in Appendix A.

Hand Searching: We will review reference lists of systematic reviews for includable literature. In addition, Technical Expert Panel (TEP) members will be asked to provide suggestions about unpublished literature.

Contacting Authors: If there is needed information regarding research methods or study results missing from the publication, or if we are aware of unpublished data, study authors may be contacted for information.

Process for Selecting Studies: The study selection criteria are pre-established (Table 1). These criteria will be used to determine eligibility for inclusion and exclusion of abstracts according to the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[34] Two team members trained in systematic review methodology will review abstracts for potential eligibility.[35] All excluded abstracts will be dual reviewed. Abstracts selected for inclusion by at least one of the reviewers will be retrieved and full-text articles will be independently reviewed for eligibility by two team members. Any disagreement will be resolved by consensus.

New literature obtained from the updated search will be dual reviewed for potential inclusion in the report and if it meets all inclusion criteria will be added to the final report.

Data Abstraction and Data Management

Data will be abstracted from studies meeting the inclusion criteria. The abstracted data will include, but are not limited to: study design, year, setting, country, sample size, eligibility criteria, population, clinical characteristics, (e.g., age, sex, race, MS, CP, or SCI), current versus potential wheelchair users, interventions and comparators, characteristics of the intervention (e.g., number of sessions, level of training of session supervisor), and outcomes (e.g., BMI, HbA1c, VO_2 max, myocardial infarction, stroke, development of diabetes, depression incidence, pulmonary function tests). Abstracted study data will be verified for accuracy and completeness by a second team member. A record of studies excluded at the full-text level with reasons

for exclusion will be reported. Systematic reviews will be reviewed for potential includable studies but will not be abstracted.

Assessment of Methodological Risk of Bias of Individual Studies

We will follow the *Methods Guide*[34] and will assess the risk of bias of randomized controlled trials and observational studies using study design-specific criteria adapted from the USPSTF[36] and the Cochrane Collaboration.[37] For randomized trials, we will assess factors such as randomization and allocation concealment methods, attrition, use of intention-to-treat methods, and blinding. For observational studies, we will assess factors such as patient selection methods; attrition; accuracy of methods for measuring exposures, outcomes, and confounders; and appropriateness of methods to address potential confounding.

Studies rated "good" have the least risk of bias, and their results will be considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

Studies rated "fair" may be susceptible to some bias, though not enough to invalidate the results. These studies may not meet all the criteria for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating will vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid.

Studies rated "poor" will have significant flaws that imply biases of various types that may invalidate the results. They may have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies will be at least as likely to reflect flaws in the study design as the true difference between the compared interventions. We will not exclude studies rated as being poor in quality a priori, but poor-quality studies will not be used in synthesizing the evidence.

Each study evaluated will be independently dual-reviewed for quality by two EPC team members and disagreements resolved by consensus.

Data Synthesis

The findings will be summarized in evidence tables indicating the study characteristics and outcome results and study quality ratings, and included in summary tables of the key findings. Study results will be reported by etiology of disability (i.e., MS, CP, SCI). Some outcomes may occur across etiologies (e.g., falls, BMI) and will be reported both overall and by etiology of disability when appropriate. Other results are specific to one etiology (e.g., autonomic dysreflexia in

SCI) and will be synthesized only for that condition. Systematic reviews will be assessed for includable studies.

The data will be synthesized qualitatively and/or quantitatively. Qualitative synthesis involves summarizing the evidence, using descriptive statistics (e.g., total number of studies, total number of participants, mean/median outcome) and identifying patterns in results according to intervention, population, and outcome measure characteristics.

Quantitative synthesis involving pooling of study findings in meta-analyses will be conducted as appropriate (i.e., when studies are homogeneous enough to provide meaningful combined estimates) in order to summarize data from multiple studies and to obtain more precise estimates. The I-squared statistic will be used to assess statistical heterogeneity. When statistical heterogeneity is present (i.e., I^2>30%) an attempt to understand the heterogeneity through stratification of data, sensitivity analysis, and/or meta-regression will be conducted. One potential sensitivity analysis is to remove lower quality studies from the analysis and compare results to an analysis of all studies.

Provided data are sufficient, there may be instances where indirect comparisons can be made for the same intervention in different populations (e.g., arm cycling in SCI vs. arm cycling in MS) or for different interventions in the same population (e.g., arm cycling vs. leg cycling in CP). We will consider indirect comparisons only when direct comparisons are not available.

Due to the large number of potential outcomes, quantitative synthesis will focus on those outcomes previously prioritized for strength of evidence rating.

Grading the Strength of Evidence

The strength of evidence for each Key Question will be initially assessed by one researcher and verified by a second reviewer for each outcome by using the approach described in the *Methods Guide*.[34] To ensure consistency and validity of the evaluation, the grades will be reviewed for:

- Study limitations (low, medium, or high level of study limitations)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)
- Reporting bias (suspected or not suspected)

The strength of evidence will be assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale by evaluating and weighing the combined results of the above domains:

- High: Very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. The findings are stable, meaning another study would not change the conclusions.
- Moderate: Moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. The findings are likely to be stable, but some doubt remains.
- Low: Limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). Additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient: No evidence, unable to estimate an effect, or have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Individual strength of evidence domains will be indicated in summary tables with ratings for the strength of evidence. Ratings for strength of evidence will be assigned for prioritized outcomes only and will focus on concepts when possible (e.g., an overall rating for depression rather than individual ratings for each depression scale). Strength of evidence ratings will be assigned by study population (i.e., MS, CP, SCI).

Assessing Applicability

Applicability will be assessed in accordance with the *Methods Guide*,[34] which is based on the PICOTS framework. Applicability addresses the extent to which outcomes associated with an intervention are likely to be similar across different patients and settings in clinical practice based on the populations, interventions, comparisons, and outcomes evaluated in the studies. For example, exclusion of adults in CP trials may render findings that are not applicable to all CP patients seen in clinical practice. Results from trials of elite wheelchair athletes may not be applicable to the average wheelchair user. Factors that may affect applicability, which we have identified a priori include eligibility criteria and patient factors (e.g., age, gender, age at injury or diagnosis, duration of injury or diagnosis, baseline fitness level, degree of wheelchair dependence, etiology of disability or potential disability), intervention factors (e.g., dose and duration of the intervention, degree of physical activity supervision), comparisons and rate in the comparison group (e.g., no physical activity, other physical activity), outcomes (e.g., clinical health outcomes, intermediate outcomes, validated or unvalidated outcomes), setting (e.g., home, community, research lab), and study design features (e.g., randomized trial versus observational study, study location). We will use this information to assess the situations in which the evidence is most relevant and to evaluate applicability to real-world clinical practice in typical U.S. settings, summarizing applicability assessments qualitatively.

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VI. Definition of Terms

Assistive technology (AT) is the term for mobility aids, (devices or equipment that can be used to help a person with a disability fully engage in life activities) such as wheelchairs, scooters, walkers, canes, crutches, prosthetic devices, and orthotic devices.

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale
6/20/2019	II. The Key Questions Page 5, Study design IV. Methods Criteria for Inclusion/Exclusion of Studies in the Review, Page 6 Table 1. PICOTS—Inclusion and exclusion criteria, Page 8, Study designs, Inclusion	The original protocol indicates specific sample sizes required for inclusion of studies for each of the three included populations: "Include for all Key Questions: Studies with the following minimum sample sizes: MS (n=30), CP (n=20), SCI (n=30). "Study sample sizes will be ≥30 for MS and SCI, and ≥20 for CP." "Studies with the following sample sizes: MS (n≥30), CP (n≥20), SCI (n≥30)."	The revised protocol will indicate a new minimum sample size for included studies of the SCI population. The proposed amendment is: "Include for all Key Questions: Studies with the following minimum sample sizes: MS (n=30), CP (n=20), SCI (n=20). "Study sample sizes will be ≥30 for MS and ≥20 for SCI and CP." "Studies with the following sample sizes: MS (n≥30), CP (n≥20), SCI (n≥20)."	Changing the sample size for SCI studies to n=20 increases the number of includable SCI studies. Careful review of the SCI studies indicates there is a paucity of studies conducted with larger sample sizes.
6/20/2019	Table 1. PICOTS—Inclusion and exclusion criteria, Page 8, Study designs, Exclusion	The original protocol states the following in the Exclusion column: "Studies published prior to 2009	The proposed edit is "Studies published before 2008"	This more clearly indicates that limiting searches to 2008 forward includes studies published in 2008.

Abbreviations: CP = cerebral palsy; NIH = National Institutes of Health; SCI = spinal cord injury; TEP = Technical Expert Panel

VIII. Review of Key Questions

National Institutes of Health ODP provided the initial Key Questions to inform their P2P Workshop. The EPC refined and finalized the Key Questions with input from AHRQ and the NIH/ODP Working Group. This input was intended to ensure that the Key Questions are specific and relevant.

IX. NIH/ODP Working Group

National Institutes of Health ODP provided input on the Key Questions, PICOTS, and inclusion criteria for studies to inform a P2P Workshop. The NIH/ODP Working Group gave feedback on the Topic Refinement, participated in monthly calls, and will participate with AHRQ, the EPC, and a Content Area Expert Group in a Webinar to refine the project scope.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after the publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers may not have any financial conflict of interest greater than $5,000. Peer

reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

Evidence-based Practice Center core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. 290-2015-00009-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ TOO reviews contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A. Literature Search Strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to February 05, 2019

RCTs and controlled observational studies

1. Spinal Cord Injuries/
2. ("spinal cord injury" or "SCI" or (spin* adj2 injur*)).ti,ab.
3. exp Multiple Sclerosis/
4. "multiple sclerosis".ti,ab.
5. Cerebral Palsy/
6. "cerebral palsy".ti,ab.
7. Disabled Persons/
8. Paraplegia/ or Quadriplegia/
9. (wheelchair or quadripleg* or parapleg* or tetrapleg*).ti,ab.
10. or/1-9
11. exp Exercise/
12. exp Exercise Therapy/
13. exp Physical Fitness/
14. Weight Lifting/
15. Yoga/
16. exp Martial Arts/
17. Equine-Assisted Therapy/
18. Bicycling/
19. Hydrotherapy/
20. exp Balneology/
21. Swimming/
22. Vibration/
23. sports/ or sports for persons with disabilities/
24. (exercise or "standing frame" or vibration or stretch* or flexibility or yoga or "martial art*" or "tai chi" or "tai ji" or hippotherapy or (equine adj2 therapy) or resistance or "weight lift*" or "weight train*" or ergometry or bicycl* or "strength train*" or treadmill or "gait train*" or swim* or aquatherapy or hydrotherapy or sport*).ti,ab.
25. ("physical fitness" or "physical activity").ti,ab.
26. or/11-25
27. 10 and 26
28. limit 27 to randomized controlled trial
29. 27 and (random* or control* or trial or cohort or group* or arm*).ti,ab.
30. 28 or 29
31. limit 30 to yr="2008 -Current"
32. limit 31 to english language

Systematic reviews

1. Spinal Cord Injuries/
2. ("spinal cord injury" or "SCI" or (spin* adj2 injur*)).ti,ab.
3. exp Multiple Sclerosis/
4. "multiple sclerosis".ti,ab.
5. Cerebral Palsy/
6. "cerebral palsy".ti,ab.
7. Disabled Persons/
8. Paraplegia/ or Quadriplegia/
9. (wheelchair or quadripleg* or parapleg* or tetrapleg*).ti,ab.
10. or/1-9
11. exp Exercise/
12. exp Exercise Therapy/
13. exp Physical Fitness/
14. Weight Lifting/
15. Yoga/
16. exp Martial Arts/
17. Equine-Assisted Therapy/
18. Bicycling/
19. Hydrotherapy/
20. exp Balneology/
21. Swimming/
22. Vibration/
23. sports/ or sports for persons with disabilities/
24. (exercise or "standing frame" or vibration or stretch* or flexibility or yoga or "martial art*" or "tai chi" or "tai ji" or hippotherapy or (equine adj2 therapy) or resistance or "weight lift*" or "weight train*" or ergometry or bicycl* or "strength train*" or treadmill or "gait train*" or swim* or aquatherapy or hydrotherapy or sport*).ti,ab.
25. ("physical fitness" or "physical activity").ti,ab.
26. or/11-25
27. 10 and 26
28. 27 and (systematic or meta*).ti,ab.
29. limit 27 to (meta analysis or systematic reviews)
30. 28 or 29
31. limit 30 to yr="2008 -Current"

Evaluation studies

1. Spinal Cord Injuries/
2. ("spinal cord injury" or "SCI" or (spin* adj2 injur*)).ti,ab.
3. exp Multiple Sclerosis/
4. "multiple sclerosis".ti,ab.
5. Cerebral Palsy/
6. "cerebral palsy".ti,ab.
7. Disabled Persons/
8. Paraplegia/ or Quadriplegia/
9. (wheelchair or quadripleg* or parapleg* or tetrapleg*).ti,ab.
10. or/1-9
11. exp Exercise/
12. exp Exercise Therapy/
13. exp Physical Fitness/
14. Weight Lifting/
15. Yoga/
16. exp Martial Arts/
17. Equine-Assisted Therapy/
18. Bicycling/
19. Hydrotherapy/
20. exp Balneology/
21. Swimming/
22. Vibration/
23. sports/ or sports for persons with disabilities/
24. (exercise or "standing frame" or vibration or stretch* or flexibility or yoga or "martial art*" or "tai chi" or "tai ji" or hippotherapy or (equine adj2 therapy) or resistance or "weight lift*" or "weight train*" or ergometry or bicycl* or "strength train*" or treadmill or "gait train*" or swim* or aquatherapy or hydrotherapy or sport*).ti,ab.
25. ("physical fitness" or "physical activity").ti,ab.
26. or/11-25
27. 10 and 26
28. (pre or before).ti,ab.
29. (post or after).ti,ab.
30. limit 27 to (comparative study or evaluation studies)
31. 27 and (28 or 29)
32. Pilot Projects/
33. pilot.ti,ab.
34. 27 and (32 or 33)
35. 30 or 31 or 34
36. limit 35 to yr="2008 -Current"
37. limit 36 to english language
38. limit 37 to randomized controlled trial
39. 37 and (random* or control* or trial or cohort or group* or arm*).ti,ab.
40. 37 not (38 or 39)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials December 2018

1. Spinal Cord Injuries/
2. ("spinal cord injury" or "SCI" or (spin* adj2 injur*)).ti,ab.
3. exp Multiple Sclerosis/
4. "multiple sclerosis".ti,ab.
5. Cerebral Palsy/
6. "cerebral palsy".ti,ab.
7. Disabled Persons/
8. Paraplegia/ or Quadriplegia/
9. (wheelchair or quadripleg* or parapleg* or tetrapleg*).ti,ab.
10. or/1-9
11. exp Exercise/
12. exp Exercise Therapy/
13. exp Physical Fitness/
14. Weight Lifting/
15. Yoga/
16. exp Martial Arts/
17. Equine-Assisted Therapy/
18. Bicycling/
19. Hydrotherapy/
20. exp Balneology/
21. Swimming/
22. Vibration/
23. sports/ or sports for persons with disabilities/
24. (exercise or "standing frame" or vibration or stretch* or flexibility or yoga or "martial art*" or "tai chi" or "tai ji" or hippotherapy or (equine adj2 therapy) or resistance or "weight lift*" or "weight train*" or ergometry or bicycl* or "strength train*" or treadmill or "gait train*" or swim* or aquatherapy or hydrotherapy or sport*).ti,ab.
25. ("physical fitness" or "physical activity").ti,ab.
26. or/11-25
27. 10 and 26
28. limit 27 to randomized controlled trial
29. 27 and (random* or control* or trial or cohort or group* or arm*).ti,ab.
30. 28 or 29
31. limit 30 to yr="2008 -Current"
32. limit 31 to english language
33. limit 32 to medline records
34. 32 not 33

Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 30, 2019

1. ("spinal cord injury" or "SCI" or (spin* adj2 injur*)).ti,ab.
2. "multiple sclerosis".ti,ab.
3. "cerebral palsy".ti,ab.
4. (wheelchair or quadripleg* or parapleg* or tetrapleg*).ti,ab.
5. (exercise or "standing frame" or vibration or stretch* or flexibility or yoga or "martial art*" or "tai chi" or "tai ji" or hippotherapy or (equine adj2 therapy) or resistance or "weight lift*" or "weight train*" or ergometry or bicycl* or "strength train*" or treadmill or "gait train*" or swim* or aquatherapy or hydrotherapy or sport*).ti,ab.
6. ("physical fitness" or "physical activity").ti,ab.
7. (1 or 2 or 3 or 4) and (5 or 6)
8. limit 7 to full systematic reviews

Database: PsycINFO 1806 to January Week 4 2019

1. spinal cord injuries/
2. ("spinal cord injury" or "SCI" or (spin* adj2 injur*)).ti,ab.
3. multiple sclerosis/
4. "multiple sclerosis".ti,ab.
5. exp paralysis/
6. ("cerebral palsy" or wheelchair or quadripleg* or parapleg* or tetrapleg*).ti,ab.
7. or/1-6
8. physical activity/ or exp exercise/
9. physical fitness/
10. yoga/
11. recreation/ or athletic participation/ or martial arts/ or weightlifting/ or sports/
12. vibration/
13. (exercise or "standing frame" or vibration or stretch* or flexibility or yoga or "martial art*" or "tai chi" or "tai ji" or hippotherapy or (equine adj2 therapy) or resistance or "weight lift*" or "weight train*" or ergometry or bicycl* or "strength train*" or treadmill or "gait train*" or swim* or aquatherapy or hydrotherapy or sport*).ti,ab.
14. ("physical fitness" or "physical activity").ti,ab.
15. or/8-14
16. 7 and 15
17. limit 16 to yr="2008 -Current"
18. limit 17 to english language
19. 18 and (random* or control* or trial or cohort or group* or arm*).ti,ab.
20. limit 18 to ("0300 clinical trial" or 2100 treatment outcome)
21. 19 or 20

Database: EBSCO CINAHL Plus with Full Text to February 6, 2019
1. (MH "spinal cord injuries")
2. TI "spinal cord injur*" OR TI sci
3. (MH "Multiple Sclerosis")
4. TI multiple sclerosis
5. (MH "Cerebral Palsy")
6. TI cerebral palsy
7. (MH "Paraplegia") OR (MH "Quadriplegia")
8. TI wheelchair OR TI parapleg* OR TI quadripleg* OR TI tetrapleg*
9. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
10. (MH "Exercise+") OR (MH "Leisure Activities+") OR (MH "Physical Fitness+") OR (MH "Physical Activity") OR (MH "Sports+")
11. (MH "Weight Lifting") OR (MH "Resistance Training")
12. (MH "Yoga")
13. (MH "Vibration")
14. TI exercise OR TI "standing frame" OR TI vibration OR TI stretch* OR TI flexibility OR TI yoga OR TI "martial art*" OR TI "tai chi" OR TI "tai ji" OR TI hippotherapy OR TI "equine therapy" OR TI "resistance train*"
15. TI "weight train*" OR TI ergometry OR TI bicycl* OR TI "strength train*" OR TI treadmill OR TI "gait train*" OR TI swim* OR TI aquatherapy OR TI hydrotherapy OR TI sport*
16. TI "physical fitness" OR TI "physical activity"
17. S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
18. S9 AND S17
19. TI random* or TI control* or TI trial or TI cohort or TI group* or TI arm*
20. AB random* or AB control* or AB trial or AB cohort or AB group* or AB arm*
21. S19 OR S20
22. S18 AND S21
23. S18 AND S21 Limiters - Published Date: 20080101-20191231; Exclude MEDLINE records

Database: Elsevier Embase Web to February 6, 2019
('spinal cord injury'/exp OR 'spinal cord injury' OR 'multiple sclerosis'/exp OR 'multiple sclerosis' OR 'cerebral palsy' OR 'disabled person' OR 'paraplegia' OR 'quadriplegia' OR 'tetraplegia') AND ('exercise' OR 'kinesiotherapy' OR 'fitness' OR 'physical activity' OR 'sport' OR 'weight lifting' OR 'yoga' OR 'martial art' OR 'hippotherapy' OR 'cycling' OR 'swimming' OR 'hydrotherapy' OR 'vibration' OR 'resistance training') AND 'article'/it AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py) AND [english]/lim AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Database: EBSCO Rehabilitation & Sports Medicine Source to February 6, 2019

1. (MH "spinal cord injuries")
2. TI "spinal cord injur*" OR TI sci
3. (MH "Multiple Sclerosis")
4. TI multiple sclerosis
5. (MH "Cerebral Palsy")
6. TI cerebral palsy
7. (MH "Paraplegia") OR (MH "Quadriplegia")
8. TI wheelchair OR TI parapleg* OR TI quadripleg* OR TI tetrapleg*
9. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
10. (MH "Exercise+") OR (MH "Leisure Activities+") OR (MH "Physical Fitness+") OR (MH "Physical Activity") OR (MH "Sports+")
11. (MH "Weight Lifting") OR (MH "Resistance Training")
12. (MH "Yoga")
13. (MH "Vibration")
14. TI exercise OR TI "standing frame" OR TI vibration OR TI stretch* OR TI flexibility OR TI yoga OR TI "martial art*" OR TI "tai chi" OR TI "tai ji" OR TI hippotherapy OR TI "equine therapy" OR TI "resistance train*"
15. TI "weight train*" OR TI ergometry OR TI bicycl* OR TI "strength train*" OR TI treadmill OR TI "gait train*" OR TI swim* OR TI aquatherapy OR TI hydrotherapy OR TI sport*
16. TI "physical fitness" OR TI "physical activity"
17. S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
18. S9 AND S17
19. TI random* or TI control* or TI trial or TI cohort or TI group* or TI arm*
20. AB random* or AB control* or AB trial or AB cohort or AB group* or AB arm*
21. S19 OR S20
22. S18 AND S21
23. S18 AND S21 Limiters - Published Date: 20080101-20191231

Appendix B. Includable Countries Rated Very High and High on the UN Human Development Index, 2018[a]

Table B-1. Includable countries rated Very High and High on the UN Human Development Index, 2018[a]

Rating	Country
Very High	Andorra
	Argentina
	Australia
	Austria
	Bahamas
	Bahrain
	Barbados
	Belarus
	Belgium
	Brunei Darussalam
	Bulgaria
	Canada
	Chile
	Croatia
	Cyprus
	Czechia
	Denmark
	Estonia
	Finland
	France
	Germany
	Greece
	Hong Kong, China (SAR)
	Hungary
	Iceland
	Ireland
	Israel
	Italy
	Japan
	Kazakhstan
	Korea (Republic of)
	Kuwait
	Latvia
	Liechtenstein
	Lithuania
	Luxembourg
	Malaysia
	Malta
	Montenegro
	Netherlands
	New Zealand
	Norway
	Oman
	Poland

Rating	Country
	Portugal
	Qatar
	Romania
	Russian Federation
	Saudi Arabia
	Singapore
	Slovakia
	Slovenia
	Spain
	Sweden
	Switzerland
	United Arab Emirates
	United Kingdom
	United States
	Uruguay
High	Albania
	Algeria
	Antigua and Barbuda
	Armenia
	Azerbaijan
	Belize
	Bosnia and Herzegovina
	Botswana
	Brazil
	China
	Colombia
	Costa Rica
	Cuba
	Dominica
	Dominican Republic
	Ecuador
	Fiji
	Gabon
	Georgia
	Grenada
	Jamaica
	Jordan
	Lebanon
	Libya
	Maldives
	Marshall Islands
	Mauritius
	Mexico
	Moldova (Republic of)
	Mongolia
	Palau
	Panama
	Paraguay
	Peru
	Saint Kitts and Nevis

Rating	Country
	Saint Lucia
	Saint Vincent and the Grenadines
	Samoa
	Serbia
	Seychelles
	Sri Lanka
	Suriname
	Thailand
	The former Yugoslav Republic of
	Tonga
	Trinidad and Tobago
	Tunisia
	Turkey
	Turkmenistan
	Ukraine
	Uzbekistan
	Venezuela (Bolivarian Republic of)

[a] Studies that do not occur in countries on this list can be excluded, exclude code: 15, non-U.S. applicable study setting