Title: National Institutes of Health Pathways to Prevention Workshop: Physical Activity and Health for Wheelchair Users

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National Institutes of Health Pathways to Prevention Workshop: Physical Activity and Health for Wheelchair Users

Abstract

Health benefits of physical activity are well recognized in the general population for reducing the risk of chronic health conditions. Less is known about the effects of physical activity on people at risk for or currently using wheeled mobility devices. On 1–3 December 2020, the National Institutes of Health (NIH) convened the Pathways to Prevention (P2P) Workshop: "Can Physical Activity Improve the Health of Wheelchair Users?" to consider the available scientific evidence on the clinical benefits and harms of physical activity for people who are at risk for or currently using a wheeled mobility device, with the aim of developing recommendations to fill gaps in the evidence base. The online workshop was cosponsored by the NIH Office of Disease Prevention (ODP), the National Center for Medical Rehabilitation Research of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Institute of Neurological Disorders and Stroke (NINDS). A multidisciplinary team of content area experts developed the agenda, and an Evidence-based Practice Center prepared the evidence report. An independent panel, selected by NIH, attended the workshop; convened to develop recommendations on the basis of the systematic review, presentations, and public comments received during the workshop; and prepared a draft report that was posted for public comment. This final report summarizes the panel's findings and identifies current gaps in knowledge. The panel made recommendations for new research efforts, including novel methods and new research infrastructure to improve the evidence base about the effects of physical activity on people at risk for or currently using wheeled mobility devices.

Approximately 65 million people worldwide require the use of wheeled mobility devices as a result of a disabling injury or illness. Physical activity, defined as any bodily movement produced by skeletal muscles that results in energy expenditure, is recommended to improve physical fitness, function, and health-related quality of life (1). Health benefits of physical activity, including associated reductions in chronic health conditions, are well recognized in the general population. A 2018 scientific report from the U.S. Physical Activity Guidelines Advisory Committee concluded that regular moderate to vigorous physical activity reduced the risk of death and many common diseases or conditions, including cardiovascular disease, stroke, hypertension, type 2 diabetes mellitus, dementia, depression, postpartum depression, excessive weight gain, and certain types of cancer (1). However, much less is known about the effects of physical activity on people at risk for or currently using wheelchairs to inform the development of evidence-based guidelines specifically relevant to these populations.

Although the population of people who are at risk for or currently using a wheeled mobility device is diverse encompassing individuals with a wide range of conditions, those with multiple sclerosis (MS), cerebral palsy (CP), or spinal cord injury (SCI) represent groups at special risk for wheelchair use and chronic health conditions. MS is a chronic inflammatory and neurodegenerative disease affecting over 700,000 people in the United States (2) and 2.1 million people worldwide (3). Worldwide prevalence estimates of CP range from 1.5 to more than 4 per 1,000 live births (4). A recent estimate suggested that the annual incidence of SCI is approximately 54 per one million people in the United States, or 17,810 new SCI cases each year (5).

On 1–3 December 2020, the National Institutes of Health (NIH) convened the Pathways to Prevention (P2P) Workshop: “Can Physical Activity Improve the Health of Wheelchair

70 Users?" to consider the available scientific evidence on the clinical benefits and harms of
71 physical activity for people who are at risk for or currently using a wheeled mobility device (e.g.,
72 manual wheelchairs, motorized wheelchairs, and motorized scooters; broadly encompassed in the
73 term 'wheelchair' in this report), with the aim of developing recommendations to fill gaps in the
74 evidence base. This report synthesizes the workshop findings and presents recommendations for
75 a variety of stakeholders (summarized in Table 1) organized around four key questions, which
76 guided both the systematic review and workshop proceedings, and three additional cross-cutting
77 themes.
78

79 **Methods**

80 The online workshop, cosponsored by the NIH Office of Disease Prevention (ODP), the
81 National Center for Medical Rehabilitation Research of the *Eunice Kennedy Shriver* National
82 Institute of Child Health and Human Development (NICHD), and the National Institute of
83 Neurological Disorders and Stroke (NINDS), was planned and implemented by a
84 multidisciplinary team of content area experts from academia, government, and the private
85 sector. A Federal Working Group developed the four key questions, coordinated the initial
86 planning, and nominated panelists and workshop presenters.

87 The Pacific Northwest Evidence-based Practice Center prepared a systematic evidence
88 review (6), which was presented at the workshop. Six panel members (authors of this article)
89 were selected by NIH as experienced researchers in the areas of public health, geriatrics, internal
90 medicine, and health disparities, with no relevant conflicts of interest. They attended the
91 workshop; convened to synthesize findings from the systematic review, presentations, and public

comments received during the workshop; and subsequently developed recommendations. The recommendations will be posted for four weeks and revised based on public comments received.

Findings

The systematic review included 141 randomized controlled trials (RCTs), 15 quasi-experimental nonrandomized trials, and seven cohort studies that addressed the benefits and harms of physical activity among MS, CP, and SCI participants. The workshop included 27 presentations and received 48 public comments during discussion periods during the workshop, through an online comment feature of the web-based conference tool. Although the systematic review included RCTs, the methodological weaknesses of those studies challenged our ability to generate robust conclusions. The presentations expanded the review to include studies that did not meet the inclusion criteria for the systematic review because the studies lacked a control group, focused on more diverse outcome measures, or did not meet the minimum 10 supervised physical activity sessions. Our findings and recommendations are summarized below by key question.

Key Questions and Recommendations

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

Since regular physical activity is known to favorably lower risk for chronic medical conditions (1), these benefits may be particularly relevant to people who are at risk for or

115 currently using wheeled mobility devices. However, among those with MS, CP, or SCI, the
116 systematic review did not identify any studies that provided evidence on the impact of physical
117 activity on cardiovascular conditions (e.g., myocardial infarction, stroke, development of
118 hypertension) or the development of diabetes or obesity. Considering that the short duration of
119 most studies challenged the ability to assess effects on chronic disease outcomes, more proximal
120 outcomes were commonly assessed as detailed below (Key Question 2).

121 *Key Question 2: What are the benefits and harms of physical activity interventions for people*
122 *who are at risk for or currently using a wheeled mobility device?*

123 While the systematic review found insufficient evidence related to the impact of physical
124 activity on chronic health conditions, other health benefits were identified for individuals with
125 MS, CP, and SCI. The systematic review found that physical activity improved walking ability,
126 function, balance, sleep, activities of daily living, female sexual function, and depression in
127 participants with MS. Physical activity also improved balance, function, and measures of
128 cardiorespiratory fitness (e.g., peak oxygen uptake) in RCTs that enrolled participants with CP.
129 While the evidence was sparse, some studies suggested that physical activity improved activities
130 of daily living, function, and aerobic capacity in participants with SCI.

131 The systematic review also delineated the effects of specific types of physical activity,
132 although the majority of this evidence was characterized as low strength. In participants with
133 MS, walking ability may be improved with treadmill training and multimodal exercise regimens
134 that include strength training. Function may be improved with treadmill training, balance
135 exercises, and motion gaming. Balance is likely improved with postural control exercises (that
136 may also reduce risk of falls) and may be improved with aquatic exercises, robot-assisted gait
137 training, treadmill training, motion gaming, and multimodal exercises. Additionally, aquatic

138 therapy may improve activities of daily living and female sexual function, and aerobic exercise
139 may improve sleep. In participants with CP, balance may be improved with hippotherapy and
140 motion gaming, and function may be improved with cycling, treadmill training, and
141 hippotherapy. In participants with SCI, some evidence suggests that activities of daily living
142 may be improved with robot-assisted gait training.

143 Workshop presenters, including elite athletes involved in adaptive sports, provided
144 anecdotes testifying to the benefits of physical activity in improving the health of people who are
145 at risk for or currently using a wheeled mobility device. They described positive effects on
146 metabolism, cardiovascular health, strength, cognition, energy, independence, social connections
147 and integration, employment, and mental health (e.g., improved life satisfaction, reduced anxiety
148 and depression).

149 The systematic review did not identify any studies focused on the harms of physical
150 activity. Thus, knowledge of possible harms was limited to the reporting of adverse events
151 (AEs), which were reported by less than 30 percent of studies. Of the studies reporting AEs,
152 falls and joint pain were the most common—additional reported AEs included muscle strain,
153 stress fracture, exacerbation of existing injuries and disease symptomology, gastric problems,
154 urinary tract infections, blisters, and bruising.

155 Other possible harms mentioned by workshop presenters included overheating,
156 autonomic dysreflexia, and fatigue. Users of wheeled mobility devices may be at special risk for
157 certain AEs. For example, users of manually-operated wheelchairs are prone to shoulder injuries
158 from overusing that muscle group. Presenters emphasized that risk for AEs must be weighed
159 against the benefits of exercise in this population and that the majority of AEs identified were
160 minor. Both the systematic review and presentations highlighted the lack of a standardized

161 approach to coding AEs to capture type, severity, timing, causality, and duration for systematic
162 analytic efforts.

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

165 There is little to no evidence that person-level factors moderate the effect of physical
166 activity interventions on benefits and harms for those who are at risk for or currently using a
167 wheeled mobility device. For most outcomes across the different types of interventions, there
168 was no variation in the effects by participant condition. The systematic review suggested that
169 participants with MS who were less ambulatory improved with core stability training, and that
170 patients with incomplete SCI who were less impaired improved with aerobic interventions.
171 However, beyond limited information on condition-specific effects, the systematic review found
172 no studies that provided findings on the benefits or harms of physical activity interventions
173 according to person-level factors such as age, sex, gender, or race/ethnicity.

174 Presenters offered some suggestions of patient factors that could moderate the effects of
175 physical activity interventions on those with MS, CP, and SCI. These moderators extend beyond
176 basic sociodemographic data and would require a more detailed understanding of patients' health
177 conditions and social context. One presenter observed that individuals with less severe injuries,
178 more recent injuries, and/or better functional status may derive greater benefit from physical
179 activity interventions compared with those who have more severe injuries, older injuries, or
180 poorer functional status. Presenters suggested that bone health, muscle structure, functional
181 status, and prior treatments are factors that could influence the relative success of any physical
182 activity intervention. The presence of comorbid conditions such as seizures, cardiovascular
183 disease, chronic kidney disease, obesity, mental health problems, cognitive/brain health, and

184 respiratory diseases may impact patients' ability to participate in and benefit from physical
185 activity. Transportation, access to equipment, the quality and fitting of the equipment, social
186 support, sex/gender intersectionality, and other social and personal factors may also influence
187 patients' ability to participate in and benefit from physical activity interventions. While the
188 presenters offered plausible causal pathways as to why these patient factors are important, there
189 are no studies that have systematically investigated them.

190 *Key Question 4: What are methodological weaknesses or gaps that exist in the evidence to*
191 *determine benefits and harms of physical activity in patients who are at risk for or currently*
192 *using a wheeled mobility device?*

193 There are substantial methodological gaps and weaknesses in the existing literature. Of
194 critical importance is the absence of clear consensus for defining and measuring physical activity
195 in users of wheeled mobility devices (e.g., intensity, frequency, duration, and mode). In regard
196 to outcomes, few studies evaluated key aspects of health, such as mental health, social
197 health/participation, cognitive function, and/or health-related quality of life. Workshop
198 presenters highlighted that the exclusion of key stakeholders (e.g., wheelchair users) from the
199 research design and implementation process resulted in a failure to adequately consider a full
200 range of outcomes that were most relevant to users of wheeled mobility devices (i.e., "what
201 matters most to me").

202 Furthermore, published studies—both represented within the systematic review and
203 discussed during the workshop—lacked common data elements (CDEs), such as those found
204 within the NIH CDE Repository (7). CDEs can be used across studies with different research
205 designs and study populations, and as a result, permit comparisons over time and between groups
206 with different conditions. The use of CDEs could facilitate the conduct of future meta-analyses

207 and provide insights into why some users of wheeled mobility devices respond to an
208 intervention, while others do not. Currently, there is no standardization of the minimal data
209 elements that should be reported in clinical trials. Studies often lack information describing: the
210 study sample (including little to no description of the control group); the intervention setting; key
211 components of the intervention (especially information about dosing and frequency/intensity of
212 physical activity); AEs; and complete information regarding the use of assistive devices (e.g.,
213 manual versus powered wheelchairs and whether the device is optimal for the user).

214 CDEs should be developed with the input of people who are at risk for or currently using
215 a wheeled mobility device. Many of the data elements in current trials were not developed for
216 users of wheeled mobility devices, and thus, may lack evidence for reliability and/or validity to
217 support their use. For example, measures derived from most traditional, wearable physical
218 activity trackers do not provide data relevant to users of wheeled mobility devices, as
219 accelerometry algorithms are based primarily on step count rather than wheelchair propulsion.
220 Even in cases where wheelchair-specific metrics are available, there is an absence of information
221 on reliability and validity to support their use in clinical research.

222 There are also several study design limitations that lessen the ability to draw strong
223 conclusions from current evidence. Studies captured in the systematic review employed small
224 sample sizes (e.g., only three studies reported greater than 100 participants) that were extremely
225 homogenous in terms of their sex/gender, age, and race/ethnicity composition, as well as their
226 level of disability (e.g., studies of CP often include younger and higher functioning participants).
227 Many trials failed to include control groups and, even when present, control groups were often
228 inadequately described, which hampered assessment of the quality of the evidence. Studies that

229 employ longitudinal designs are critical to capture variability and assess longer-term health
230 outcomes.
231 In addition, the systematic review was striking in the absence of more innovative study
232 designs, which could accelerate the pace of understanding while maintaining methodologic rigor.
233 For example, employing a Sequential Multiple Assignment Randomized Trial (SMART) design
234 (8) to develop an adaptive intervention could balance the need for sample heterogeneity with the
235 need for scientific rigor.
236
237 ***Cross-Cutting Themes and Recommendations***
238 Over the course of the workshop, discussions, and public comments, the panelists
239 identified three cross-cutting, intersecting themes with relevance to physical activity for people
240 at risk for or currently using a wheeled mobility device that were not specifically captured in the
241 systematic review or in any single presentation: "What Matters Most" to users of wheeled
242 mobility devices; Translation of Research into Practice; and Research Infrastructure.
243 *Theme 1: "What Matters Most"*
244 Research efforts to date have been narrow in focus and impact, failing to capture what
245 matters most to patients who are at risk for or using wheeled mobility devices, and their families,
246 caregivers, and health care providers (e.g., maintaining independence, addressing pain, or simply
247 "being a good dad"). The panelists challenge researchers to consider outcomes that are more
248 meaningful to these individuals. Researchers should consider outcomes that enhance patients'
249 ability to participate in physical activity in their homes and local community. Patients value their
250 independence and ability to interact with others. Thus, researchers need to approach the health
251 and social needs of patients who are at risk for or currently using a wheeled mobility device with

252 a broader lens. It is also important to consider the perspectives of other stakeholders including
253 spouses, children, other family members, caregivers, and health care providers. The impact of
254 interventions on patients and these stakeholders will influence whether they are adopted and
255 incorporated into the lifestyles of patients. There was a consensus among the panelists that
256 individuals who currently use a wheeled mobility device need "a seat at the table" when
257 decisions are being made about prioritization of research questions and research design,
258 including the intervention to be tested, in whom it will be tested, how it will be implemented, and
259 the types of outcomes assessed.

260 It is also apparent that persons most severely ill or with more advanced disability are
261 often excluded from studies. This is in part due to the types of interventions studied and the
262 outcomes that researchers are aiming to achieve, which restricts study samples to healthier
263 patients. However, this limits the potential impact and generalizability of the research.

264 *Theme 2: Translation of Research into Practice*

265 The current evidence-based physical activity interventions for wheelchair users cannot be
266 readily scaled-up and implemented in real-world settings. Factors that limit the translation of
267 evidence-based interventions include highly select groups of study participants who do not
268 reflect populations at risk for or currently using a wheeled mobility device; tightly controlled
269 interventions tested in lab-based settings; specialized equipment not readily available outside of
270 the research context; and the lack of consideration of real-world issues such as insurance
271 coverage and reimbursement challenges. To increase the translational potential of interventions
272 and accelerate the timeline from research to its incorporation into practice, the panel
273 recommends that researchers consider the foundational concepts of implementation science (i.e.,

274 diffusion, dissemination, implementation, adoption, and sustainability) (9) at the earliest stages
275 of research planning.

276 As emphasized under Theme 1, meaningful engagement of stakeholders in the
277 intervention design process, including patients, providers and caregivers, will facilitate the
278 development of interventions that are feasible and acceptable to a broader range of individuals
279 and in a wider range of settings. Consistent with an implementation science perspective, it is
280 critical to increase the diversity of study participants. Research has typically focused on
281 homogeneous samples with low severity of disease and functional impairment, and high levels of
282 readiness for change, leading to challenges in generalizing study findings to underrepresented
283 populations including those with more severe limitations and/or at earlier stages of readiness
284 (i.e., "pre-intenders"). Finally, the potential for scale-up must be considered at all key decision
285 points in the research process. Intervention components that are cumbersome and resource
286 intensive should be avoided—those with the potential to expand intervention reach (e.g., virtual
287 or tele-health options) should be prioritized.

288 *Theme 3: Research Infrastructure*

289 One of the overarching themes from the workshop was a call for a more robust national
290 research infrastructure to support studies of physical activity for people at risk for or currently
291 using a wheeled mobility device. There are a number of important ways to achieve this goal.
292 The panel calls for standardized outcome measures to allow for harmonization of data across
293 studies. The panel recommends the development of a national data repository that would foster
294 the collection of CDEs from all physical activity research studies focused primarily on people
295 who are at risk for or currently using a wheeled mobility device. Such a repository would help
296 mitigate the existing limitations of current research that focuses primarily on small sample sizes

297 by allowing for researchers to pool data. Funding opportunities are also needed to promote
298 research that spans agencies and institutes in order to foster multisite and multidisciplinary
299 collaboration. Such synergistic efforts are needed to support larger studies to capture the long-
300 term impact of physical activity on the health of users of wheeled mobility devices. Finally, an
301 investment is needed in the training of the next generation of researchers. Standardized curricula
302 and accessibility to mentorships will help ensure that the next generation of scientist-
303 practitioners is prepared to pursue research that will meet the needs and maximize health
304 outcomes for users of wheeled mobility devices.
305

306 **Conclusions**

307 Although some efforts have been made to expand the evidence base regarding the effects
308 of physical activity for people at risk for or currently using wheeled mobility devices, the
309 existing evidence is limited. This presents challenges in creating physical activity guidelines
310 that, if followed, are both effective and safe. Lessons learned from the systematic review and
311 workshop indicate that further progress will require larger, more ambitious, and more inclusive
312 research efforts, including RCTs and observational studies to assess short-term as well as long-
313 term outcomes. We encourage a greater emphasis on outcomes that "matter most" to users of
314 wheeled mobility devices, in contrast to those that seem most easily measured by researchers.
315 Further, we strongly endorse the need for a coordinated, national research agenda focused on the
316 effects of physical activity for people at risk for or currently using wheeled mobility devices.
317 This will require an adequately funded research infrastructure to foster multisite and multi-
318 disciplinary studies employing novel methods and including underrepresented populations as

study participants. Only through such concerted and sustained efforts will genuine progress be achieved.

322 Table 1: Summary of workshop panel recommendations for future research according to the key
323 questions to address physical activity for people who are at risk for or currently using a wheeled
324 mobility device
325

Key Questions	**Recommendations**
Key Question 1: What is the evidence base on physical activity interventions to prevent obesity, diabetes, and cardiovascular conditions in people who are at risk for or currently using a wheeled mobility device?	1. Include users of wheeled mobility devices in population-based, prospective observational studies with measures of physical activity and health outcomes. 2. Conduct longitudinal observational studies examining the risk of developing chronic conditions (e.g., cardiovascular disease, diabetes, and obesity) over time among those who are at risk for or currently using a wheeled mobility device. 3. Incorporate symptom burden (e.g., pain and fatigue), functional decline, and health-related quality of life measures in longitudinal observational studies. Quantify burden of disease measures (e.g., healthy life expectancy, years of life lost, years lived with disability, disability adjusted life years) as part of the health outcomes assessed (10). 4. With evidence from RCTs and longitudinal observational studies, develop evidence-informed physical activity guidelines specific to patients who are at risk for or currently using a wheeled mobility device.
Key Question 2: What are the benefits and harms of physical activity interventions for people who are at risk for or currently using a wheeled mobility device?	1. Quantify the benefits and harms of physical activity on long-term health outcomes among patients who are at risk for or currently using a wheeled mobility device. 2. Assess the importance of equipment and technology, including muscle stimulation therapies. 3. Diversify outcomes to assess how factors such as cognition, mental health, and negative experiences (e.g., injury, perceived burden) are linked with study participation. 4. Examine the role of health literacy for the effectiveness of interventions. 5. Include individual and family/caregiver-level outcomes. 6. Compile more comprehensive information on adverse events (AEs), applying validated definitions that allow for data harmonization across studies. Information on AEs should include type, severity, timing, duration, and assessment of causality.
Key Question 3: What are the patient factors that may affect the benefits and harms of physical activity in	1. Consider the role of age, sex, gender, and intersectionality in developing a research agenda on the benefits and harms of physical activity interventions for patients who are at risk for or currently using a wheeled mobility device.

patients who are at risk for or currently using a wheeled mobility device?	2. Use community-based participatory research approaches to engage a more representative population to produce generalizable research findings that can lead to meaningful health benefits. 3. Promote studies that span all levels of functional status and disease severity. Studies that focus on Gross Motor Function Classification System (GMFCS IV-V) populations and patients with more severe MS, CP, and SCI are especially needed. 4. Conduct studies to assess the impact of physical activity on "universal health outcomes" (11) including symptom burden (e.g., pain and fatigue), functional decline, and health-related quality of life in patients who are at risk for or currently using a wheeled mobility device—overall and according to patient-level factors. 5. Include samples that capture the full spectrum of users of wheeled mobility devices, including those with the highest-level injuries. 6. Consider sedentary behavior, which may modify the impact of physical activity, such that wheelchair users with co-occurring high physical activity and high sedentary behavior may be at greater risk for adverse health outcomes than those with high physical activity and low sedentary behavior. 7. Conduct studies that ensure inclusion across the lifespan. 8. Develop tele-studies to ensure greater access to the full spectrum of users of wheeled mobility devices.
Key Question 4: What are methodological weaknesses or gaps that exist in the evidence to determine benefits and harms of physical activity in patients who are at risk for or currently using a wheeled mobility device?	1. Develop valid and reliable measures to assess physical activity among diverse samples of users of wheeled mobility devices. 2. Promote study designs that evaluate dosing and intensity of physical activity for people who are at risk for or currently using a wheeled mobility device. 3. Employ common data elements (CDEs) across studies of physical activity for users of wheeled mobility devices. 4. Focus on adapting/developing consumer grade devices that can reliably capture physical activity for users of wheeled mobility devices, especially with regard to capturing the duration and intensity of physical activity. 5. Assess longer interventions and/or longer maintenance periods following interventions. Scrutinize whether an inactive control group is ethical. Consider alternative control conditions to provide benefit to enrolled participants. 6. Assess mechanisms of effect (e.g., fitness, depression, sleep, pain, fatigue, blood pressure). 7. Conduct clinical trials based on impairments and functional deficits rather than just underlying diagnosis and pathology.

	8. Identify and measure mediators, moderators, and process measures, as well as behavioral change techniques in interventions and incorporate behavioral change theory into interventions. 9. Consider rigorous study designs to assess adaptive interventions (12) (e.g., SMART). 10. Lengthen the typical intervention period of 6–12 weeks as indicated by the systematic review and track outcomes beyond the immediate intervention period in order to capture variability and assess longer-term health outcomes. 11. Design larger studies with more diverse, multisite enrollment to enhance generalizability of the research.

References

1. **2018 Physical Activity Guidelines Advisory Committee.** 2018 Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC: U.S. Department of Health and Human Services; 2018. Accessed at https://health.gov/sites/default/files/2019-09/PAG_Advisory_Committee_Report.pdf on 29 December 2020.
2. **Wallin MT, Culpepper WJ, Campbell JD, et al.** The prevalence of MS in the United States: A population-based estimate using health claims data. Neurology. 2019;92:e1029-e1040. [PMID: 30770430] doi: 10.1212/wnl.0000000000007035
3. **Dilokthornsakul P, Valuck RJ, Nair KV, et al.** Multiple sclerosis prevalence in the United States commercially insured population. Neurology. 2016;86:1014-1021. [PMID: 26888980] doi: 10.1212/wnl.0000000000002469
4. **Centers for Disease Control and Prevention.** Data and Statistics for Cerebral Palsy; 2019. Accessed at www.cdc.gov/ncbddd/cp/data.html on 29 December 2020.
5. **National Spinal Cord Injury Statistical Center.** Spinal cord injury facts and figures at a glance. Birmingham, AL: University of Alabama at Birmingham; 2020. Accessed at https://www.nscisc.uab.edu/Public/Facts%20and%20Figures%202020.pdf on 12 January 2021.
6. Physical activity and the health of wheelchair users: A systematic review of evidence in people with multiple sclerosis, cerebral palsy, and spinal cord injury. Draft comparative effectiveness review. Rockville, MD: Agency for Healthcare Research and Quality; 2020. Accessed at https://effectivehealthcare.ahrq.gov/products/physical-activity-wheelchair/protocol on 12 January 2021.
7. **U.S. National Library of Medicine.** NIH Common Data Elements (CDE) Repository. Accessed at https://cde.nlm.nih.gov/home on 29 December 2020.
8. **Lei H, Nahum-Shani I, Lynch K, et al.** A "SMART" design for building individualized treatment sequences. Annu Rev Clin Psychol. 2012;8:21-48. [PMID: 22224838] doi: 10.1146/annurev-clinpsy-032511-143152
9. **Rapport F, Clay-Williams R, Churruca K, et al.** The struggle of translating science into action: Foundational concepts of implementation science. J Eval Clin Pract. 2018;24:117-126. [PMID: 28371050] doi: 10.1111/jep.12741
10. **Roth GA, Mensah GA, Johnson CO, et al.** Global burden of cardiovascular diseases and risk factors, 1990-2019: Update from the GBD 2019 study. J Am Coll Cardiol. 2020;76: 2982-3021. [PMID: 31727292] doi: 10.1016/j.jacc.2020.11.010
11. **Working Group on Health Outcomes for Older Persons with Multiple Chronic Conditions.** Universal health outcome measures for older persons with multiple chronic conditions. J Am Geriatr Soc. 2012;60:2333-2341. [PMID: 23194184] doi: 10.1111/j.1532-5415.2012.04240.x
12. **Pallmann P, Bedding AW, Choodari-Oskooei B, et al.** Adaptive designs in clinical trials: Why use them, and how to run and report them. BMC Med. 2018;16:29. [PMID: 29490655] doi: 10.1186/s12916-018-1017-7