



Review article

Lessons learned from clinical trials of exercise and physical activity in people with MS – guidance for improving the quality of future research



Robert W. Motl^{a,*}, Bo Fernhall^a, Kevin K. McCully^b, Alexander Ng^c, Mathew Plow^d,
Lara A. Pilutti^e, Brian M. Sandroff^f, Kathleen M. Zackowski^g

^a Department of Kinesiology and Nutrition, College of Applied Health Sciences, University of Illinois Chicago, 1919 W. Taylor St, Chicago, IL 60612, USA

^b Department of Kinesiology, Mary Frances Early College of Education, University of Georgia, Athens, GA, USA

^c Department of Physical Therapy, College of Health Sciences, Marquette University, Milwaukee, WI, USA

^d Frances Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, OH, USA

^e Interdisciplinary School of Health Sciences, University of Ottawa, Ottawa, ON, Canada

^f Center for Neuropsychology and Neuroscience Research, Kessler Foundation, West Orange, NJ, USA

^g Research, National Multiple Sclerosis Society, New York, NY, USA

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ABSTRACT

The body of research on exercise and physical activity among persons with multiple sclerosis (MS) has expanded rapidly in quantity, but not necessarily quality, over the past 20+ years. There is evidence for beneficial effects of exercise and physical activity on immune cells and neurotrophic factors, brain structure and function, walking and cognitive performance, fatigue, depression, and pain, and quality of life among persons with MS. Nevertheless, there is heterogeneity in the outcomes of exercise and physical activity, and a recognition of substantial challenges for improving the effectiveness of those behaviors in MS. To move the field forward, members of the National MS Society physical wellness research working-group pooled collective experiences for identifying challenges, logistic complexities, and opportunities for researchers in designing and conducting interventions of exercise and physical activity among persons with MS. We examined the scope of our experiences and identified collective “lessons learned” regarding the behaviors themselves; study design features and stage of research; study setting, safety, and sample selection; and implementation of randomized controlled trials (RCTs) and treatment fidelity. This paper provides a resource that can inform researchers, particularly new investigators or established investigators transitioning into MS, on conducting high-quality RCTs on exercise and physical activity in MS.

1. Introduction

There has been an exponential increase in the volume of research on exercise and physical activity behaviors among persons with multiple sclerosis (MS) over the past 20+ years (Dalgas et al., 2020). To date, research from randomized controlled trials (RCTs) has established the benefits of those behaviors across a range of International Classification of Functioning, Disability and Health outcomes (Motl and Pilutti, 2012). This includes beneficial effects on immune cells and neurotrophic factors, brain structure and function, walking and cognitive performance, symptoms of fatigue, depression, and pain, and quality of life among persons with MS (Motl and Pilutti, 2012; Motl et al., 2017). The evidence has supported calls for Exercise as Medicine in MS (Dalgas et al., 2019)

and resulted in guidelines for the prescription of exercise and physical activity behaviors (Kalb et al., 2020). There is further recognition that exercise and physical activity behaviors are safe with seemingly few side-effects for persons with MS (Pilutti et al., 2014). Nevertheless, there is within and between study heterogeneity in the outcomes of exercise and physical activity behaviors among persons with MS (Baird and Motl, 2019), and further recognition of substantial challenges (e.g., small, underpowered studies with a poorly defined exercise training stimulus tested for improving exploratory outcomes in a sample that is not prescreened and enrolled for a specific problem)(1–3) that need to be resolved for improving the state of knowledge on the effectiveness of exercise and physical activity in people with MS (Motl et al., 2018). The generation of a stronger knowledge base will be essential from an

* Corresponding author.

E-mail address: robmotl@uic.edu (R.W. Motl).

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implementation science perspective for the application and integration of research evidence into practice (evidence-based practice) and public health policy for impacting the lives of persons with MS.

The body of research on exercise and physical activity behaviors among persons with MS has expanded rapidly in quantity (Dalgas et al., 2020), but not necessarily quality (e.g., continued adoption of small, under-powered RCTs of poorly designed exercise stimuli with general MS samples) (Motl et al., 2017). To move this field forward, members of the National MS Society physical wellness research working-group, along with two outside members who have extensive exercise in exercise and MS, have pooled collective experiences for identifying challenges, logistic complexities, and opportunities for researchers in designing and conducting RCTs of exercise and physical activity behaviors among persons with MS. We examined the scope of our experiences and identified collective “lessons learned” regarding the behaviors themselves; study design features and stage of research; study setting, safety, and sample selection; and implementation of RCTs and treatment fidelity. This paper pools expert opinions based on a modified Delphi approach and (a) provides a resource that can inform researchers, particularly those who are new investigators or established investigators transitioning into MS, on the perils and pitfalls of RCTs in this area based on our collective experiences, and (b) identifies paths forward in overcoming such problems. This effort addresses the National MS Society physical wellness research working-group’s goal of mentoring/training both junior and new, but established researchers in the area of exercise and physical activity, and improving the quality of future research with the objective of positively impacting those living with MS (Motl et al., 2018). We see this as key from an implementation science perspective for the successful application and integration of research evidence into practice and policy.

2. Scope of experiences

We met “virtually” on multiple occasions over a 2-year period and broadly discussed our experiences and the field of research regarding RCTs of exercise and physical activity in MS. The content of these meetings was annotated by the first and last authors and then refined and collated by all authors into our collective experiences that represented the eight thematic categories listed in Table 1. The process followed a modified Delphi process of iterative discussion and progression through repeated rounds of voting until reaching group consensus on all themes and content. The authors further identified and articulated the nature of each issue and its importance per category, and then provided a possible strategy or approach that would guide future research on exercise and physical activity in MS. The thematic categories and content were then reviewed by two researchers from outside the National MS Society physical wellness research working-group (LAP and BMS) with extensive experience in MS and exercise who identified points for clarification and elaboration. Those points were addressed by the members of the National MS Society physical wellness research working-group, and resulted in the final thematic categories and content agreed on by all that are outlined in the next eight sections of the paper. All authors, including members of the National MS Society physical wellness research working-group and two outside researchers, agreed on the content of the final paper.

2.1. Behavior of interest

There are standard and historical definitions of physical activity, exercise, and physical fitness (Table 2) that have been broadly applied in research among the general population and those living with chronic disabling diseases and conditions (Caspersen et al., 1985). Nevertheless, those terms are often applied interchangeably in research involving persons with MS, and this can create conceptual ambiguity among healthcare providers when moving the research into clinical practice. This might further contribute toward the conceptual ambiguity in

understanding the terms among people with MS (Kinnett-Hopkins et al., 2019), and undermine public health strategies for adoption and promotion of exercise and physical activity behaviors among this population. To that end, researchers should adopt a standard language for defining the behavior under investigation (Table 2) and further report how the intervention itself aligns with the precisely-defined behavior of interest. Such definitions will further inform selection of outcomes, prescriptions, and dosing of the behavior itself (e.g., frequency, intensity, time, and type or FITT principle components for exercise training) (Schlagheck et al., 2021), as the emerging research informs clinical practice and public health promotion. This focus on defining the behavior of interest collectively will be important for generating good, hypothesis-driven research questions that can be tested using strong research designs and informing clinical practice and public health promotion.

2.2. Study design features

The field has increasingly moved toward RCTs when examining the benefits and associated mechanisms of exercise and physical activity in MS. Nevertheless, not all RCTs are created equal, and features of the study design, including control group/condition or dependent variables, influence the study outcomes and response heterogeneity, and ultimately the veracity of conclusions supporting the translation from research into practice. Researchers should be mindful of appropriate selection of control conditions that isolate non-exercise features of interventions (e.g., social contact in groups and/or attention from session leaders), as this better isolates the outcomes (i.e., benefits or mechanisms) of exercise and physical activity in MS. Researchers should be aware that comorbid conditions might confound the results of RCTs (Fakolade et al., 2016), and that non-MS control groups can inform our understanding of specificity/generalizability of outcomes. Researchers should further be mindful of decisions regarding selection of outcome variables (e.g., primary vs. secondary outcomes; generic vs. disease targeted measures; and psychometrically-sound outcomes based on previous research or perhaps a core set of outcomes), reporting on behavior change techniques (e.g., inclusion as a focus of RCT itself or a means of achieving the desired outcomes), and identifying factors influencing response heterogeneity (e.g., measurement intervals, manipulation checks, and blinded outcomes) for informing precision trials that optimize the transition from research into practice. Researchers might consider opportunities for integrating patient perspectives when designing trials as this could influence the long-term, broad-scale uptake of exercise and physical activity by those with MS. Patient engagement in the design of RCTs will be key for developing a stronger body of research with direct impact on patients themselves and perhaps faster uptake amongst persons with MS and healthcare providers. Of further importance, researchers should pre-register clinical trials (e.g., on ClinicalTrials.gov) and publish protocol papers (Feinstein et al., 2020), and further adopt reporting standards such as CONSORT, STROBE, and TIDieR (Hoffman et al., 2014). Such actions are critical considering recent concerns regarding (a) the reproducibility of science (Munafa et al., 2017) and (b) the observation that most published research findings may actually be false (Ioannidis, 2005). This is essential for improving the reliability and efficiency of science, and strengthening the credibility of the published scientific literature (Munafa et al., 2017; Ioannidis, 2005).

2.3. Stage of research

There is a continuum of the stages of experimental research that spans feasibility (T0) through pilot (T1), efficacy (T2), and effectiveness (T3), and adoption into clinical practice (T4); see papers for examples of feasibility (Adamson et al., 2016), pilot (Edwards et al., 2018), efficacy (Dalgas et al., 2009), and effectiveness (Motl et al., 2019) trials. Researchers should clearly identify a phase of the spectrum when planning,

Table 1

Thematic categories of lessons learned within the field of research regarding randomized controlled trials of exercise and physical activity in MS.

Topic	What is/are the issue(s)?	Why is this issue important?	What is the strategy or approach for overcoming the issue?
1. Behavior of Interest	The terms exercise and physical activity are related, but not the same, and often are reported as synonymous in randomized controlled trials (RCTs).	The lack of differentiation of terms creates confusion among researchers, clinicians, organizations, and persons with MS when moving from research into practice/implementation. The terms have different approaches for description (e.g., Frequency, Intensity, Time, Type [FITT] principle for exercise or steps/day for physical activity), measurement (e.g., adherence, compliance, sustainability) and dosing, and this directly informs prescription in future applications into clinical practice.	Researchers should clearly identify, define, and report the behavior under investigation and align/harmonize it with the intervention for all study protocols. This includes the FITT principle for exercise, as well as metrics of adherence and compliance with the intervention program. There is a need for providing metrics of intensity (e.g., rate of perceived exertion) that might bridge the gap between exercise training and free-living physical activity. The measurement of outcomes regarding the behavior of interest must match with the behavior under investigation (e.g., adherence/compliance vs. free-living physical activity). The prescription of exercise and physical activity should be guided based on appropriate and ongoing assessments such as aerobic capacity and muscle strength for exercise training, and step rates or activity counts for physical activity. There should be a clear plan for capturing and reporting the dose of exercise training and/or physical activity for informing translation.
2. Study Design Features	There is limited consideration of study design features, including mechanisms and response heterogeneity, in the planning, delivery, and reporting of clinical trials of exercise and physical activity in MS.	The features of the study design (e.g., control group, control condition, outcome variables) influence the veracity of conclusions regarding clinical trials of exercise and physical activity in MS. For example, exercising in a group with a leader might result in putative benefits with exercise and physical activity that are actually associated with social contact and/or attention. The mechanisms of behavior change with physical activity or beneficial outcomes with exercise training are often unknown, but inform future applications in clinical practice. There is heterogeneity (i.e., response variability) in the outcomes of physical activity and exercise training interventions that influences the precision of intervention application in clinical practice.	Researchers should account for and isolate non-exercise features of the treatment condition such as social contact, attention, and movement itself through administration of an appropriate control condition (e.g., stretching in a small group with a coach for group based exercise). Researchers should systematically measure and examine the influence of possible confounding factors (e.g., comorbidity) and associated differential effects of conditions after randomization. Researchers might consider the inclusion of non-MS control groups for identifying the unique effects of exercise and physical activity in MS. Researchers should include appropriate and acceptable outcomes, including potential mechanisms and disease-specific outcomes, when conducting clinical trials of exercise training in MS. Researchers should identify strategies and techniques for promoting behavior change, adherence, and sustainability when conducting clinical trials of physical activity in MS. Researchers should identify and measure a range of factors that might influence response heterogeneity for the design of precision-based trials (SMART designs). Researchers should pre-register clinical trials and publish protocol papers, as well as adopt appropriate reporting guidelines/criteria for producing reliable and credible science.
3. Stage of Research	There is a lack of defining, reporting, and justifying stages of the research continuum when moving from feasibility (T0) through pilot (T1), efficacy (T2), and effectiveness (T3) research involving exercise and physical activity in MS.	The stage of research has clear implications for interpreting the study results and meaning, and moving through stages of the continuum results in foundations of knowledge and experiences for informing the design and execution of sequential research studies and adoption into clinical practice and communities (T4).	When necessary, researchers should consider feasibility trial designs (T0) as a starting-point for studies involving exercise and physical activity in MS, as this provides experiences with the population, intervention, outcomes, and trial logistics as learning lessons before an efficacy trial. Researchers should consider pilot trial designs (T1) with control conditions for establishing effect sizes for sample size estimates and drop-out rates for powering subsequent efficacy research (T2). The design and delivery of an efficacy trial design (T2) will provide strong data for meeting guidelines, such as American Academy of Neurology (Gronseth et al., 2017), for level of evidence that informs clinical application of exercise and physical activity in MS. The delivery of effectiveness research designs (T3) will provide data on exercise and physical activity programs when moved from a controlled or laboratory setting into less controlled and community environments for establishing real-world intervention effects.

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Table 1 (continued)

Topic	What is/are the issue(s)?	Why is this issue important?	What is the strategy or approach for overcoming the issue?
4. Study Setting	The existing research on exercise and physical activity in MS is often performed in tightly-regulated laboratory and clinical environments, and these might not translate into less supervised and regulated home or community settings.	There are often problems encountered when translating research from tightly-regulated laboratory and clinical-rehabilitation environments into non-supervised, community settings, including residential settings (e.g., unique features of home or community settings, levels of supervision, and cultural relevancy).	Researchers might consider the final disposition of the exercise and physical activity program for persons with MS when starting initial research trials (e.g., walking on a treadmill might translate into walking over-ground in the community). Researchers might consider the delivery and monitoring of the exercise stimulus when starting initial research trials (e.g., steps per unit time and other real-world outcomes rather than treadmill walking speed might translate into walking over-ground in the community). Researchers should clearly describe the environment and degree of supervision, for example, for replication and translation. Researchers should consider the potential application of exercise/physical activity interventions through physical rehabilitation clinics and settings as part of current and future health care models.
5. Safety	There is still broad concern regarding the safety of exercise and physical activity in MS.	The lack of information on the safety of exercise and physical activity in MS creates confusion among researchers, clinicians, organizations, and persons with MS when considering adopting a new behavior regimen.	Researchers should create a plan for monitoring, recording, and vetting all adverse and serious adverse events in RCTs of exercise and physical activity in MS. Researchers should adopt clear definitions for reporting the existence of all adverse and serious adverse events even if deemed unanticipated and/or unrelated with exercise or physical activity itself. This should include reporting and documentation of approaches for mitigating the potential of such events, especially if the approaches were successful. Researchers should partner with clinicians and gather feedback from people with MS for defining, tracking, and monitoring the occurrence and impact of exacerbations (or increases in symptoms that persist over time).
6. Sample Selection	The existing samples enrolled in exercise and physical activity research lack diversity regarding race, ethnicity, age, level of disability, and disease type, as examples, and further are infrequently recruited and enrolled based on the presence of a focal problem (e.g., fatigue); there further is exclusion of persons with comorbidities.	The lack of diversity (e.g., sex, race, rural/urban location, etc.) limits generalizability of the results broadly in MS, and the lack of focal inclusion criteria based on a targeted problem limits the application of research results for clinical treatment and practice. The exclusion of samples with comorbid conditions limits generalizability amongst people with MS, as vascular comorbidity is often exclusionary, but prevalent.	Researchers must develop detailed recruitment plans based on the demographics of MS for generating samples that promote diversity, inclusion, and generalizability of the study results. Researchers should develop research protocols that focus on a targeted, primary end-point (e.g., depression) and recruit and enroll samples with presence of that focal end-point or problem (e.g., major depressive disorder). There should be consideration of new and appropriate approaches for screening for inclusion/exclusion based on comorbidity, and balancing the risks with safety monitoring and intervention delivery with higher-risk samples. There should be a concerted effort on training workshops and best-practice manuals for exercise and physical activity research in MS, and this could be developed from existing publications in medical rehabilitation (Bamman et al., 2018). There should be opportunity for consultation between new investigators and established researchers in the design of clinical trials involving exercise and physical activity in MS. The development and delivery of large trials fitting the criteria of T3 and T4 stages of research will likely require multi-site interventions, and emphasis should be placed on collaboration and training new investigators in team and implementation science.
7. Implementation of Randomized Controlled Trials	There are few resources for new investigators or established investigators newly engaged in exercise and physical activity research for MS on the execution of clinical trials (e.g., planning, recruiting, delivery, monitoring, and outcomes).	The lack of experiences on logistics of trials or nuances of MS may create challenges for the proper execution of strong clinical trials of exercise and physical activity in MS, and this may create avoidable problems causing conflicting results in the scientific literature that erode confidence in the application of exercise and physical activity.	

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Table 1 (continued)

Topic	What is/are the issue(s)?	Why is this issue important?	What is the strategy or approach for overcoming the issue?
8. Treatment or Intervention Fidelity	There are very few applications of fidelity monitoring for supporting the internal and external validity of a research study and its outcomes in the area of exercise and physical activity in MS.	Fidelity involves the degree to which an intervention is delivered as planned or intended, and factors such as varying treatment dose and provider training, among others, can influence intervention delivery and study outcomes.	<p>Researchers should consider adopting the published recommendations for incorporating treatment fidelity practices into health behavior research, as proposed by the National Institutes of Health Behavior Change Consortium (Bellg et al., 2004).</p> <p>Researchers should consider protocol papers addressing the NIH BCC guidelines by including five areas, namely (a) study fidelity protocol, (b) fidelity of study design, (c) fidelity of provider training, (d) fidelity of delivery of treatment, and (e) fidelity of receipt of treatment.</p> <p>Researchers should clarify when interventions include behavior change strategies and techniques, and if the inclusion is part of the intervention program itself or represents an examination of effectiveness for behavior change.</p> <p>Researchers should design the strongest trial designs that permit the publication of null/negative results.</p>

conducting, and reporting research on exercise and physical activity in MS. This is important as many studies in MS straddle the stages of research, and this creates challenges in interpreting the data and implementation of outcomes into clinical care. The stage of research has clear implications for hypothesis generation, and interpreting and contextualizing the study results. Sequentially moving through stages of the continuum results in foundations of knowledge and experiences for informing the design and execution of research studies and adoption into clinical practice and application in communities. The stage of research further informs decisions on recruitment, sample size, power, control condition, and outcomes, and sets researchers on a trajectory for maximizing the potential for successful lines of research that translate into clinical practice and communities. The stage of research even aligns with decisions on classes of evidence appropriate for levels of therapeutic recommendations in clinical practice based on guidelines such as those provided by American Academy of Neurology (Gronseth et al., 2017).

2.4. Study setting

The majority of research on exercise and physical activity in MS has been undertaken in supervised and controlled settings, namely tightly-

Table 2
Standard definitions of physical activity, exercise training, and physical fitness.

Term	Definition
Physical activity	Any bodily movement that is produced by contraction of skeletal muscles and that substantially increases energy expenditure above resting level. This can include active physical leisure (i.e., leisure-time physical activity), exercise, sport, occupational work, and household chores.
Exercise training	Subset of leisure-time physical activity that is planned, structured, and repetitive with a specific external objective of improving or maintaining one or more components of physical fitness. This can be described based on the frequency, intensity, time, and type of such activity.
Physical fitness	Characteristics of a person that permit a good performance of a given physical task in a specified physical, social, or psychological environment. This can include health-related fitness (i.e., components affected by habitual physical activity and that related with health status) and performance-related fitness (i.e., components that permit individual athletic competition and that have limited relationship with health). There are five components of fitness namely morphological, muscular, motor, cardiorespiratory, and metabolic.

Note. Definitions adopted from Caspersen et al. (1985).

regulated laboratory and clinical environments, yet there are substantial limitations of reach and scalability with such research. There are problems encountered when translating research from tightly-regulated laboratory and clinical-rehabilitation environments into non-supervised, community settings, including residential settings (e.g., unique features of home or community settings, levels of supervision, cultural relevancy; lab vs. remote outcomes) and there is substantially less research involving home-based and/or community-based exercise training and physical activity programs in MS (Ghahfarrokhi et al., 2021). To that end, researchers should be aware of the desired final setting of the exercise and physical activity program for persons with MS when starting initial research trials (T0 and T1 stages of research), and further consider implications of approaches for delivering and monitoring the stimulus when moving across study settings; there further is a need for integrating remote screening and data collection along with remote delivery of interventions. There should be clear reporting on the environment (e.g., lighting and temperature) and degree of supervision/monitoring, and consideration of how interventions could ultimately be delivered by healthcare providers through physical rehabilitation clinics.

2.5. Safety

There has been a historical concern regarding the safety of exercise training and physical activity in persons with MS based on early observations of a transient blurring of vision with thermogenesis (i.e., Uthhoff’s syndrome), coined exercise-induced amblyopia, and the notion that exercise-induced thermogenesis might be harmful for the disease and its progression (White et al., 2000). We actually know very little about the safety of these behaviors in MS, as nearly 50% of RCTs do not record/report the occurrence of adverse events and serious adverse events in the context of exercise training and physical activity interventions with MS (Pilutti et al., 2014), yet this is a focus for further clarity through an ongoing systematic review and meta-analysis (Learnmonth et al., 2021). The lack of accurate information on the safety of exercise and physical activity in MS creates confusion among researchers, clinicians, organizations, and persons with MS when considering adopting a new behavior regimen. Researchers should create or adopt standard plans for monitoring, recording, and vetting all adverse and serious adverse events in RCTs of exercise and physical activity in MS, as is done for RCTs addressing pharmaceutical interventions regulated by the Food and Drug Administration (Ahmad, 2003) and examining treatments for psychological disorders (Duggan et al., 2014). This will be facilitated by adoption of clear definitions of adverse and serious

adverse events, even if the events are deemed unanticipated and/or unrelated with exercise and physical activity. This can be extended into the study of relapses in MS, and researchers should document methods for mitigating adverse and serious adverse events in RCTs of exercise and physical activity. The clear documentation and reporting of adverse and serious adverse events is pivotal for the broad-scale promotion of exercise and physical activity by healthcare providers in MS (Sandroff et al., 2021). However, we should not let the fear of potential adverse events limit the design and implementation of RCT for people with MS, as such risk is out-weighted by the potential benefits.

2.6. Sample selection

One of the largest, field-wide problems with RCTs of exercise and physical activity in MS involves sample selection and parameters. The samples enrolled in existing exercise and physical activity research lack diversity regarding sex, race, ethnicity, age, level of disability, and disease type (Lai et al., 2018), yet there are some notable exceptions regarding the race/ethnicity of the study samples (Kinnett-Hopkins and Motl, 2018; Baird et al., 2019). The samples further are infrequently recruited and enrolled based on pre-screening for the presence of a focal problem (e.g., severe fatigue or major depressive disorder), level of physical activity, or experience with the outcome measures (e.g., neuro-performance outcomes); this represents a mismatch between inclusion/exclusion criteria and intervention outcomes. There is often exclusion of persons with comorbidities, particularly vascular comorbidities as putative risk factors for exercise testing and training and physical activity participation (Bisson et al., 2017). This severely restricts generalizability of results from RCTs across MS (i.e., inclusion/exclusion factors for screening) and into clinical practice, and limits our understanding of exercise and physical activity as treatments for focal problems in MS. This further limits our understanding of demographic and clinical variables, including comorbidities, that moderate the outcomes of RCTs, as these might explain response heterogeneity (Baird and Motl, 2019). Ultimately, this limits the adoption and inclusion of exercise and physical activity in the clinical management of MS. Researchers should consider developing recruitment plans based on the population demographics of MS and thereby generating samples that permit generalizability of the study results, and should focus on a targeted, primary end-point (e.g., depression) and recruit and enroll samples with presence of that focal end-point or problem (e.g., major depressive disorder). Researchers might consider new approaches for screening of inclusion/exclusion based on comorbidities, or develop data analysis plans that examine the effects of comorbid conditions on trial outcomes. Researchers should develop plans for balancing risks with safety monitoring and intervention delivery among samples with high risk or contra-indications for exercise testing and exercise training and physical activity prescription. Researchers must include recruitment strategies that promote inclusion of underrepresented groups in clinical research involving exercise and physical activity in MS (Erves et al., 2017), as this is mandated by funding agencies in the United States (e.g., NIH) through detailed recruitment strategies for reaching underrepresented groups in clinical research and improving the generalizability of research. This could be strengthened through partnerships with organizations such as the Accelerated Cure project and its MS Minority Research Engagement Partnership Network as a multi-stakeholder network for defining and addressing the issue of racial/ethnic minority underrepresentation in MS research. This will result in heterogeneity in samples and perhaps concerns with erroneous conclusions regarding intervention outcomes, and therefore necessitates subgroup analysis as part of appropriately powered intervention trials that will require extensive funding and appropriate data analysis plans. Such efforts will broaden our understanding of the effects of exercise and physical activity in MS.

2.7. Implementation of RCTs

The success of building a stronger body of knowledge on exercise and physical activity in MS depends, in part, on recruiting new researchers into this area of study. Nevertheless, there are few resources for new investigators, or established investigators newly engaged in exercise and physical activity research for MS, to learn appropriate design, planning, and execution of clinical trials (e.g., planning, recruiting, delivery, monitoring, and outcomes). This lack of experience with the logistics of implementing clinical trials and/or lack of understanding the nuances of MS may create challenges for the design and execution of strong RCTs of exercise and physical activity in MS. This may further create avoidable problems causing conflicting results in the scientific literature that erode confidence in the application of exercise and physical activity. We propose concerted efforts on training workshops and best-practice manuals for exercise and physical activity research in MS, and this could be facilitated through existing publications in medical rehabilitation (Bamman et al., 2018). There should be opportunities for consultation between new investigators and established investigators and clinical partners in the design of trials involving exercise and physical activity in MS. This can ensure greater success in multi-site interventions that involve large trials guided by T3 and T4 stages of research for establishing evidence supporting the application of exercise and physical activity in the clinical treatment of MS; see protocol papers for examples of seemingly well designed trials using appropriate designs (Feinstein et al., 2020; Motl et al., 2019; Sandroff et al., 2019, Sandroff et al., 2019; Griffith et al., 2015; Plow et al., 2012). The training necessary for implementing RCTs might be afforded through workshops and institutes on conducting clinical trials by the NIH, and we further emphasize the importance of specific behavioral science clinical trials training by organizations such as the Society for Behavioral Medicine.

2.8. Treatment fidelity

The National Institutes of Health Behavior Change Consortium (NIH BCC) has underscored the importance treatment and intervention fidelity in the design and delivery of RCTs (Bellg et al., 2004), and this is applicable in trials of exercise and physical activity in MS. This is important as fidelity involves the degree to which an intervention is delivered as planned or intended, and recognizes that factors such as varying treatment dose and provider training, among others, can influence intervention delivery and study outcomes. RCTs among people with MS can be complicated, based on the presence of 'bad days', occurrence of life events, and fluctuating symptoms, and can require flexibility in the delivery of the RCT, even if it reduces the fidelity of the trial. Nevertheless, there are few reports of fidelity monitoring for supporting the internal and external validity of a research study and its outcomes in the area of exercise and physical activity in MS. Researchers might consider adopting the published recommendations for incorporating treatment fidelity practices into health behavior research, as proposed by the NIH BCC (Bellg et al., 2004) and recently applied in MS (Silviera et al., 2019). We encourage researchers to publish protocol papers for the overall trial and address the NIH BCC guidelines by including five areas, namely (a) study fidelity protocol, (b) fidelity of study design, (c) fidelity of provider training (i.e., ensuring that trainer/coaches are consistent in training and experience), (d) fidelity of delivery of treatment (i.e., ensuring that trainer/coaches are consistent in delivering treatments), and (e) fidelity of receipt of treatment. This will provide credible information for supporting the highest quality of evidence from RCTs of exercise and physical activity in persons with MS, and may permit the publication by journals of null/negative results for understanding when interventions are not successful; this is incredibly important given the current crisis with reproducible science in clinical trials (14.). We provide example papers reporting null outcomes for the primary aim of RCTs examining exercise training in MS (Sandroff et al., 2019; Baquet et al., 2018; Oken et al., 2004; Riemenschneider et al., 2021).

2.8.1. Summary

The study of exercise and physical activity in persons with MS is growing in scope and quantity, but requires focal direction for shaping its evolution into the highest-quality and most impactful body of science for translation into clinical practice and public health promotion. Hence, we pulled together our collective experiences regarding exercise and physical activity research in persons with MS, and identified eight themes for advancing future research that aligned with the behaviors themselves, study design features and stages of research; study setting, safety, and sample selection; and implementation and treatment fidelity. We provided a description and review of the eight themes and associated issue(s), importance, and solution(s) as a “resource” that can inform researchers, particularly those who are new investigators or established investigators transitioning into MS, on the perils and pitfalls of clinical trials in this area. We further believe that these eight themes have direct relevance for the greater vision of supporting exercise and physical activity in the management of MS as a disease as well as its biological, functional, symptomatic, and quality of life outcomes, but we do not consider our paper as providing consensus recommendations. We recognize that research involving exercise and physical activity in MS is an evolving field and that our perspectives identify current issues through our experience and knowledge of the literature, and we hope that, as additional studies are completed, these themes will be continually refined by investigators in the MS community. We recommend that investigators consider and address the themes we outlined herein with the awareness that each study, with positive or negative findings, provides more information to better understand the impact of exercise and physical activity among people in MS.

We believe this paper makes an important contribution and provides a first step in outlining a roadmap that addresses the goals of the National MS Society physical wellness working-group toward training/mentoring junior and new researchers in the area of exercise and physical activity (Motl et al., 2018), and improving the veracity of future research for better impacting those living with MS. We recognize the caveat that our group only included researchers from North America, and the views of clinicians, policy makers, funders, and people with MS are important for shaping future research on exercise in MS. Nevertheless, over time and in the presence of continued and expanded funding, we anticipate that a stronger body of research will result in the broad inclusion of exercise and physical activity within the clinical armamentarium of healthcare providers who manage MS (Motl and Pilutti, 2012; Sandroff et al., 2021; Benito-Leon, 2011). Such a perspective aligns with implementation science wherein there is an urgent need for the application and integration of research evidence into practice (evidence-based practice) and public health policy for impacting the lives of persons with MS.

Declaration of Competing Interest

The authors report no conflicts of interest regarding this paper, and there was no source of funding for this paper.

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