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*Research Article*

# A Tripartite Knowledge Translation Program: Innovative Patient-Centered Approach to Clinical Research Participation for Individuals with Multiple Sclerosis

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*Background*. Knowledge translation (KT) models that represent an individual's perspective are a sign of effective KT. Some common challenges in KT include participant engagement, organization of the team, and time demands of the participants. We implemented a unique tripartite KT program to (1) share current research, (2) inform persons living with multiple sclerosis (pwMS) about the clinical research process, and (3) invite pwMS to immediately participate in clinical research. The primary aim was to determine participants' perspectives on the value and acceptability of an experiential research program offered at a patient and family educational conference. *Methods*. A team of researchers identified factors that would impact the logistics of hosting an experiential research program at a conference and designed a unique tripartite KT program. The local multiple sclerosis (MS) society was engaged to select an appropriate location and invite stakeholders to the conference. A survey to determine participants' perspectives on the value and acceptability of the experiential research program was developed and analyzed. *Results*. 65 pwMS attended the conference, and 44 (67.7%) participated in the on-site experiential research program. 72.7% of the participants completed the survey, of which 93.8% stated that they strongly agree or agree with the following statements: "Did you feel like participating in research today was a valuable experience to you?" and "Did you feel like you were contributing to MS research?" 100% of the participants agreed or strongly agreed when asked "would you like to see more research activities taking place at these kinds of events?" *Conclusions*. This paper describes the logistics and challenges of conducting an experiential KT program, which proved to be rewarding for pwMS. The majority of pwMS attending the conference agreed to participate in the on-site experiential research program and an overwhelming majority of participants felt the experience was valuable.

## 1. Introduction

Knowledge translation (KT) is defined by the Canadian Institutes of Health Research (CIHR) as "a dynamic and interactive process that includes the synthesis, dissemination, exchange, and ethically sound application of knowledge to improve health, provide more effective health services and products, and strengthen the health care system." [1] An effective KT strategy should consider the micro perspective of an individual, apart from the environmental organizational view [2]. There are many KT frameworks and theories, which can be a challenge to implement [3, 4]. KT models that

take into account a user's perspective are indicative of effective KT [5]. Participants who better understand the research process through experiential learning may feel differently about the value of clinical research. Experiential learning is the process of learning through experience. The association for experiential education has defined the experiential education as "a teaching philosophy that informs many methodologies, in which educators purposefully engage with learners in direct experience and focused reflection in order to increase knowledge, develop skills, clarify values, and develop people's capacity to contribute to their communities" [6]. Many factors influence how clinical research findings could be used by various stakeholders in evidence-informed decision-making [7–9]. Challenges of implementing KT from clinical research include participant or community engagement, organization of the research team, and time requirements of the participants. To address these challenges, we implemented a unique experiential tripartite KT program to (1) share current research, (2) inform persons living with multiple sclerosis (pwMS) about the clinical research process, and (3) invite interested pwMS to participate in clinical research through experiential learning at a patient and family educational conference sponsored by the Multiple Sclerosis (MS) Society of Canada. The aims were to determine participants' perspectives on the value and acceptability of an experiential research program and describe a process for developing such a program at a patient and family conference setting.

## 2. Materials and Methods

The Office of the Saskatchewan MS Clinical Research Chair was contacted by the Saskatchewan (SK) division of the Multiple Sclerosis Society of Canada (MSSC) to identify researchers to present their data in a traditional didactic setting for the "MS Connects" annual conference. The MS Connects conference is designed to bring together pwMS and caregivers, healthcare professionals, and researchers to discuss the latest advancements in MS research and symptom management. A brain-storming session identified a unique KT opportunity by using both didactic presentations and clinical research at an on-site interactive research space embedded within the conference. The goal of this project was to make the clinical research process transparent to pwMS and to actively engage the community in the research process. Considering the interest pwMS and their caregivers had shown in contacting our office about research opportunities, this would be a valuable endeavor. Further discussion regarding the logistics of hosting an event in which pwMS would participate in a research protocol at the conference identified the following components (Table 1): ethical approval, a location accessible to people with disabilities for both the didactic presentations and the data collection, preconference information to attendees regarding the opportunity for research participation during the conference, onsite provision of information to potential participants, identifying a research question that could be answered in a single visit, recruitment and training of the research team, obtaining the tools needed to perform the data collection, the layout of the conference space for conducting research (physical space for privacy, consent, participant scheduling, equipment and personal), obtaining consent, maintaining privacy, participant flow, and identification of potential bottlenecks at the conference. The study coordinator sourced all equipment needed for data collection identified by the research team and contacted the venue for equipment rental (tables/chairs/-drapery, etc.). Team members were identified, and roles were assigned to spearhead individual components based on their expertise (Table 2).

The Saskatchewan Division of the MSSC helped to facilitate the plan and was responsible for securing the appropriate venue and inviting people living with MS and other

Table 1: Logistics required for the knowledge translation program.

| |
|---|
| (i) Preconference |
| (a) Ethical approval |
| (b) Accessible location for persons with disabilities |
| (c) Education about how an interactive research space works |
| (d) Identifying a research question that can be answered in one visit |
| (e) Recruitment and training of the research team |
| (f) Identifying a unified data input tool (REDCap) |
| (g) Layout |
| (h) Documentation of participation at each research activity |
| (i) Advertising the conference |
| (ii) At the conference |
| (a) Education on clinical research and KT and how to participate |
| (b) Obtain consent |
| (c) Maintain privacy |
| (d) Flow of participants |
| (e) Data entry and collection |
| (f) Identify potential bottlenecks |
| (iii) Equipment required for the interactive research space; item (number) |
| (a) Name tags |
| (b) Signage |
| (c) Tables and chairs |
| (d) Curtain divides and privacy screens |
| (e) Easels and boards for research posters |
| (f) Participant study cards |
| (g) Printed consent forms |
| (h) Participant satisfaction surveys |
| (i) 9-HPT (3) |
| (j) ARAT (3) |
| (k) Master list |
| (l) iPads (5) |
| (m) Laptops for 9-HPT (3) |
| (n) Laptops for ARAT (3) |
| (o) Extension cords (6) |
| (p) Hand sanitizer (10) |
| (q) Sanitizing wipes (2) |
| (r) Hole punch (9) |

Table 2: Number of team member(s) assigned to a specific role/research activity.

| Role/activity | Number of team member(s) |
|---|---|
| Study coordinator (organize all preconference activities, lead role at conference) | 1 |
| Assistant coordinator (assist study coordinator, particularly at the conference) | 1 |
| Hand out study cards and assign research participant number | 2 |
| Obtain consent and assist with questionnaires (MSQoL-54 and UEFS) | 5 |
| Conduct 9-HPT | 3 |
| Conduct ARAT | 3 |
| Technical support | 1 |
| Obtain survey | 2 |
| Total number of research team | 18 |

Abbreviations: MSQoL-54: multiple sclerosis quality of life-54; 9-HPT: 9-Hole Peg Test; ARAT: Action Research Arm Test; UEFS: Upper Extremity Function Scale.

stakeholders to the MS Connects conference. Upon approval by the MSSC, the clinical researchers identified a research project that could be suitable to be conducted at the conference setting and began the application for ethical approval. *We designed a project that emphasized active patient participation, which was based on the review of the existing literature and the researchers' experience. With this in mind, the team designed a research study that was relevant to individuals with MS, could be completed in a single visit, would be doable in the physical space of the venue, and would be fun for prospective participants to complete.* The approved research protocol, entitled "*A*ction *R*esearch Arm Test in *MS*" ("AR(MS)"), involved the assessment of upper extremity function, which is a significant source of disability, in pwMS. Upper extremity impairment hinders the ability of pwMS to perform activities of daily living and decreases their quality of life [10]. At the conference, we evaluated three different measures of upper extremity function: the Upper Extremity Function Scale (UEFS, a patient-reported outcome measure (PROM)), the Action Research Arm Test (ARAT), and the 9-Hole Peg Test (9-HPT), to determine which best correlates with the quality of life (QoL), as measured by the multiple sclerosis (MS) quality of life-54 (MSQoL-54) questionnaire. *The measurement of upper extremity functions and their correlation with quality of life might provide a better understanding of the disability level of patients in daily living tasks and could contribute to better planning of rehabilitation programs. We hypothesized that the multimodal ARAT may better correlate with the quality of life and the UEFS, than the 9-HPT. A peer-reviewed manuscript (based on the results of the main research study) entitled "A Descriptive Correlational Study to Evaluate Three Measures of Assessing Upper Extremity Function in Individuals with Multiple Sclerosis" was submitted to the Multiple Sclerosis International journal, which provides a detailed assessment of the data generated from this conference and our clinic.* All data were collected using REDCap, a secure web-based software platform designed to support data capture for research [ 11, 12].

Ethics approval was obtained from the University of Saskatchewan's Biomedical Research Ethics Board (Protocol BIO 484). In discussions with the SK Division of the MSSC and the University of Saskatchewan's Biomedical Research Ethics Board, it was agreed that conference attendees should be given prior knowledge that the experiential research would be part of the day's events, in addition to the speaker presentations. After ethics approval, the conference was advertised on websites and social media platforms sponsored by the MSSC. To maintain confidentiality, the MSSC sent letters of invitation and information about the on-site experiential research study to pwMS and their caregivers who signed up for the conference. *The letter of invitation described the identity of the principal investigator, the purpose of the study, the study activities, the approximate time required to participate, that the data collected would be kept confidential and stored securely, and that the study was voluntary (with the requisite withdrawal from participation information). Also included in the letter was the contact information for the study coordinator so that prospective participants could contact her for detailed information about the study. The Research Ethics Office of the University of Saskatchewan reviewed and approved the invitation letter, which gave prospective participants the option to discuss their rights as a participant with an unbiased party*. Next, the floor plan of the event including the lecture space and the interactive research space was designed in collaboration with the SK division of the MSSC, lead investigators, coordinators, and venue staff (Figure 1). *It was mandatory for our team members to attend orientation and training sessions prior to the conference, which provided instruction on the proper administration of the 9-HPT and ARAT, how to properly enter data into REDCap, and manage participant flow at the event.* A research team package with a detailed description of all the activities and information was developed and distributed among the team members before the training sessions. The package also contained information on the venue, parking, timings, contact details, food and beverage, and duties assigned to the individual team members. Core team members met regularly to troubleshoot any identified barriers and test-run the protocol. Team T-shirts and name tags were designed for our team members, who arrived at the venue at a scheduled time before the start of the conference to set up their respective stations.

First, participants learned about different research topics through didactic lectures. Next, a didactic lecture reviewed the research process using the experiential learning

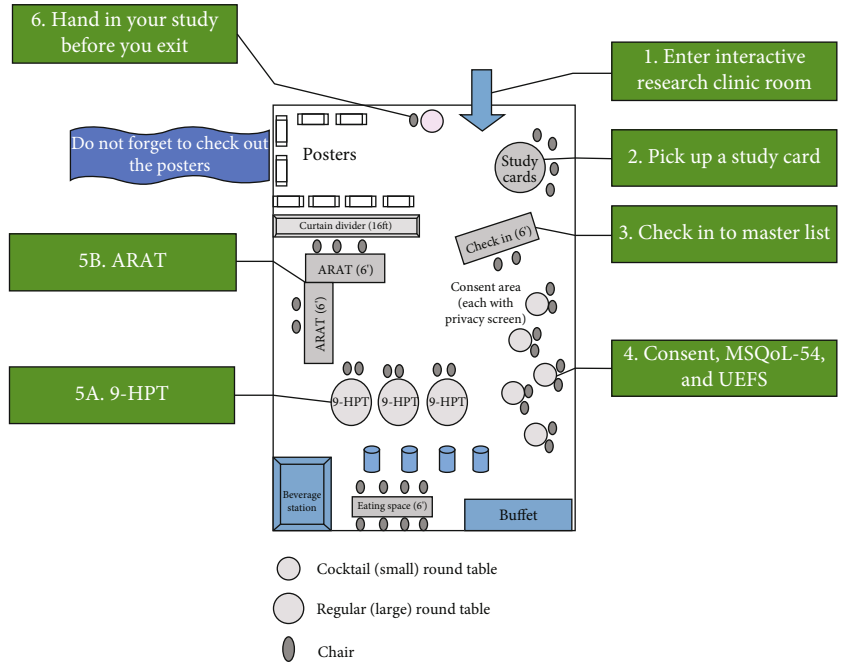


Figure 1: Layout of the interactive research space. Abbreviations: MSQoL-54: multiple sclerosis quality of life-54; 9-HPT: 9-Hole Peg Test; ARAT: Action Research Arm Test; UEFS: Upper Extremity Function Scale.

conference project as an example study. Finally, participants were invited to partake in research at the conference, providing experiential learning, and a convenience sample of research participants was recruited from the attendees of the conference. MS researchers were selected and invited for the KT didactic presentations, which included oral lectures on stem cell therapy for MS, cannabinoids for the treatment of MS symptoms, MS research in Saskatchewan, and a novel immunotherapeutic approach for treating MS. In addition, local MS research trainees were asked to share their research via poster presentation accessible to all attendees. The research presentations were designed to provide attendees the opportunities to learn and engage with experts in the field. Following the research presentations, Michael C. Levin, M.D., the Saskatchewan Multiple Sclerosis Clinical Research Chair, gave a presentation titled "What Is Clinical Research and How to Participate in it Today." This talk used lay language to define research, clinical research, and KT. This was followed by a detailed description of the informed consent process as well as a page-by-page review of the consent form and all of the research activities required to participate in the research protocol at the conference. He also introduced the team, which included a neurologist, a physiatrist, two physiotherapists, a nurse practitioner, nurse educators, clinic/research coordinators, a public health specialist, and research staff. *The timing of the presentation was such that prospective participants were educated about the study before being invited to participate. We arranged for the experiential research space to be open throughout the day, which gave participants plenty of time to participate. Our study team members at the consent stations also explained the consent form and answered any question individually, with dividers and appropriate spacing between stations, thus assuring patient privacy and providing ample opportunity to clarify any part of the research project*. The participants were informed that if they choose to participate in the study, there is a small chance that the upper limb mobility tasks may cause fatigue. However, all of the tasks occur while sitting, and there are medical professionals on hand if necessary. They were also informed that they may feel uncomfortable with some of the items in the questionnaires and they are welcome to answer only those they are comfortable with.

Figure 1 illustrates the layout of the interactive research space. Upon entering the interactive research area, the prospective participant was provided a study card with a unique participant identifier and a list of study activities (consent and questionnaires, 9-HPT, and ARAT). All prospective participants then checked in with a team member stationed at the check-in table. This team member was responsible for confidentially maintaining the master list with the names of participants and unique identifiers. All team members at various stations had electronic devices (computer or iPad) to collect data and were trained to log onto REDCap for entering participant's unique identifier prior to recording data. The instruments on REDCap were designed to allow confidential signing of consent mandatory prior to data fields opening for entry. After the team member confirmed the prospective participant was willing to participate in the study, they were directed to one of the five consent stations.

Each consent station was surrounded by a privacy screen and staffed by a qualified research team member. Following the electronic signature of the consent form with a stylus, participants filled out demographic information (month/year of birth, sex, year of first MS symptoms, year of MS diagnosis, MS phenotype, and current use of MS disease-modifying therapies) followed by the UEFS and the MSQoL-54. Our

project was designed on REDCap in a way that the UEFS could be completed only after finishing the demographic questions and the MSQoL-54 questionnaire. Our team members assisted the participants with the tablet at the consent station and provided any other assistance required during their participation in the interactive research space. Once all the items were completed at the consent station, team members punched a hole in the study card labeled with "consent and questionnaires" as confirmation of completing this step of the study. Without having the hole punch to say that they had consented, they were unable to participate in any other study activity.

Participants were then directed to the upper extremity measurement area that included three 9-HPT and three ARAT stations. Each station was staffed by a research team member trained on administering the specific upper extremity test. *While designing the study, we took into consideration the layout of the room and the conference activities. We enabled participants to choose the activity with the shortest line, withdraw from participation at any point, and allowed participants to come and go as they pleased from the study area to attend the conference presentations. Our research team tracked participants via a study card, which was hole-punched by a team member after completion of each study activity.* Participants either self-randomized by choosing which upper extremity measure they wanted to do first or were randomized based on the availability of testing stations. For example, the first few participants were able to choose to begin with either the 9-HPT or ARAT, while subsequent participants went to the remaining unoccupied test station. Prior to testing, the participants provided the examiner with their study ID on their study card. The researcher logged into the participant's specific REDCap portfolio for data recording. Participants were instructed to return the hole-punched study card to our team members and invited to complete the participant satisfaction survey. This survey aimed at evaluating the participants' perspectives on the value and acceptability of an experiential research program *that consisted of consenting for research, filling the questionnaires on REDCap instruments (demographic, the MSQoL-54, and the UEFS), and completing the 9-HPT and ARAT*. The survey consisted of questions using a five-point Likert scale: 1 = strongly agree, 2 = agree, 3 = no opinion, 4 = disagree, and 5 = strongly disagree. Throughout the day, participants had the opportunity to review research posters, interact with our clinical research team, and ask questions related to clinical research.

## 3. Results

Sixty-five pwMS attended the conference, and 44 individuals (67.7%) participated in the on-site experiential research program. Of the 44 participants (32 females and 12 males, mean age = 49.1 ± 11.5 years, mean disease duration (in years) = 14.8 ± 13.08, 32 (72.7%) participants with relapsing-remitting MS, four with secondary progressive MS, six with primary progressive MS, and two with progressive-relapsing MS) who were consented, one participant chose not to visit 9-HPT and ARAT stations. Thirty-two participants (72.7%) completed the participant satisfaction survey (Table 3). Thirty participants (93.8%) strongly agreed or agreed with the following statements: "Did you feel like participating in research today was a valuable experience to you?" and "Did you feel like you were contributing to MS research?" Six participants (18.8%) agreed or strongly agreed to the question "Did you feel like there was too much going on and not enough time to do it all?" The majority of participants ($n = 31$; 96.9%) indicated they felt that their rights as a participant were respected and valued. Of the 31 participants who responded to the question "At any point were you uncomfortable (physically or emotionally) participating in the research activities?", 30 participants (96.8%) disagreed or strongly disagreed with that question. All of the participants (100%) agreed or strongly agreed when asked "Would you like to see more research activities taking place at these kinds of events?"

## 4. Discussion

These data show that an experiential research opportunity was found to be acceptable and valued by pwMS attending a KT event. We also realized that the logistics of developing this type of event were feasible. We believe this approach is an effective and novel approach to KT for pwMS, and this type of program can be applied to other human diseases. There are several community participation KT frameworks, but they tend to be generic and may not take into account contextual aspects of inclusive KT [13–17]. There are only a few studies that have presented KT frameworks for the creation of evidence-based online resources for pwMS. Hill et al. started the IN-DEEP (integrating and deriving evidence, experiences, and preferences) project to produce easily accessible and meaningful evidence-based health information that could be utilized by pwMS for decision-making and self-management. Their project involved a mixed-methods approach of conducting focus groups with pwMS and their families to develop a model for presenting evidence-based information, which was later reviewed and finalized by all key stakeholders before being uploaded online and evaluated [18]. Likewise, Synnot et al. conducted a 2-phased mixed-method project for producing an evidence-based treatment information website in collaboration with pwMS. Phase 1 included review panels with pwMS and healthcare professionals to test treatment summaries (paper-based) before developing and pilot testing the website. Phase 2 included an online survey after launching the website to gather user feedback [19]. This study was limited by incomplete data ascertainment which was also observed in our study. Both of these projects described a partnership approach to developing online evidence-based information for pwMS, but these approaches lacked an experiential learning opportunity.

In this project, our team designed and successfully implemented an experiential research opportunity at a KT conference setting applicable to pwMS. This example of experiential research was useful in translating and sharing evidence-based information with key knowledge users. It could enhance comprehension and understanding of clinical

Table 3: Results of the participant satisfaction survey.

| Question(s) ($n$ = total number of participants who responded to the question) | Number of participants | | | | |
|---|---|---|---|---|---|
| | Strongly agree | Agree | No opinion | Disagree | Strongly disagree |
| Did you feel like participating in research today was a valuable experience to you? ($n = 32$) | 25 | 5 | 1 | 0 | 1 |
| Did you feel like you were contributing to multiple sclerosis research? ($n = 32$) | 27 | 3 | 2 | 0 | 0 |
| Would you like to see more research activities taking place at these kinds of events? ($n = 32$) | 29 | 3 | 0 | 0 | 0 |
| Did you feel like there was too much going on and not enough time to do it all? ($n = 32$) | 3 | 3 | 8 | 7 | 11 |
| Do you feel like your rights as a participant were respected and valued? ($n = 32$) | 28 | 3 | 1 | 0 | 0 |
| At any point were you uncomfortable (physically or emotionally) participating in the research activities? ($n = 31$) | 0 | 0 | 1 | 1 | 29 |

research, which might lead to an increase in future engagement. It can also aid in bridging the gap between researchers and patients and potentially accelerate transformative changes in MS research that are appealing to pwMS. Community participation could also help individuals develop their knowledge, skills, and confidence to improve and gain control over the conditions that may affect their lives [20]. Importantly, pwMS and their family members are increasingly becoming active users of health information [21] and may value experiential learning opportunities. Therefore, our approach could be instrumental in improving the quality and relevance of KT for pwMS and their family members. The fact that we received positive feedback from the majority of participants suggests that we may have successfully addressed some of the common challenges in KT.

While pwMS shared that participating in experiential research combined with didactic sessions was valued, this project had a few limitations. *The use of convenience sampling might have introduced selection bias in our study. This convenience sample included individuals with MS who were active members of the MSSC or visiting the society's website and/or social media platforms and were more likely to attend the conference and volunteer for our experiential research study.* Twenty-seven percent of the participants did not complete the exit participant satisfaction survey. Incomplete data ascertainment could lead to an over- or underestimate of participant satisfaction levels. Six participants also indicated that they agreed or strongly agreed to the question "Did you feel like there was too much going on and not enough time to do it all?" These results support that some people found the study protocol challenging to complete in the time allotted. Participants were requested to complete patient demographic and quality of life survey data immediately following the consent process. This portion of the experiential research protocol took a fairly long time and involved sustained attention. Moreover, the MSQoL-54 questionnaire in itself requires considerable time to complete and could be challenging for individuals with MS suffering from fatigue. In a study conducted by Yozbatıran et al. to assess the motor function of upper extremity function and its relation with fatigue, cognitive function, and quality of life in pwMS, three patients were not able to complete a study task due to excessive fatigue and their data was excluded from the study [10]. To overcome this limitation, we could have provided flexibility to the participants for completing the questionnaires on REDCap at their convenience. Perhaps if we had scheduled a break between the consent process and the questionnaires, this may have been even more acceptable to participants. However, participants completed all aspects of the study protocol, except for one participant who did not complete all the upper limb tests, suggesting sufficient time allotted to complete this aspect of the protocol. *Another limitation is that we did not engage and consult pwMS during the design of the project. Our team had approximately three months from the initiation of the idea to the execution of the event. On reflection, if we were to host another experiential research program, we would give ourselves 6-12 months and consult individuals living with MS during the development phase.* Finally, this project did not evaluate factual knowledge gained by participants about the research process or factual knowledge gained from the didactic research topics presented. Further research would be needed to evaluate the extent of factual knowledge gained about the research process through experiential learning combined with or compared to didactic sessions alone. Considering the cost-effectiveness and accessibility of digital and remote technologies, a hybrid or a virtual model may be feasible and bring pwMS and their care providers together with researchers and health professionals from across the globe. The consent process and patient-reported outcome measures are also feasible remotely. Such endeavors could provide a more efficient and user-friendly platform for the current and future research.

## 5. Conclusions

The logistics of conducting an experiential research KT event was feasible, and pwMS found the experience rewarding. Onsite experiential research program preceded by didactic sessions provided a highly acceptable platform that facilitated interactions between knowledge users and creators. The majority of pwMS attending the conference agreed to participate in the experiential research program, and an overwhelming majority of participants felt the experience was valuable and should be continued.

## Data Availability

The data used to support the findings of this study are available within the article.

## Conflicts of Interest

The authors declare that there is no conflict of interest.

## Authors' Contributions

Aman Saini and Colleen Cochran share equal credit for the work presented.

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*Research Article*

# A Descriptive Correlational Study to Evaluate Three Measures of Assessing Upper Extremity Function in Individuals with Multiple Sclerosis

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*Background*. Activities of daily living and quality of life (QOL) are hindered by upper extremity (UE) impairments experienced by individuals with multiple sclerosis (iMS). The Nine-Hole Peg Test (9-HPT) is most frequently used to measure UE function. However, it does not measure peoples' ability to perform routine tasks in daily life and may not be useful in iMS who cannot pick up the pegs utilized in the 9-HPT. Therefore, we evaluated three measures to explore a more comprehensive assessment of UE function: Upper Extremity Function Scale (UEFS), Action Research Arm Test (ARAT), and the 9-HPT. The objectives were to quantitatively assess the relationship between these measures of UE function, understand if the measures correlate with QOL as calculated by the MS Quality of Life-54 (MSQOL-54), and to determine differences in the measures based on employment status. *Methods*. 112 (79 female) iMS were prospectively recruited for this descriptive correlational study. Inclusion criteria were as follows: confirmed diagnosis of MS or clinically isolated syndrome, age ≥ 18 years, and ability to self-consent. All statistical analyses including Spearman's correlation coefficient ($r_s$) and Kruskal-Wallis tests were performed using SPSS. *Results*. A moderate correlation ($r_s = -0.51$; $p < 0.001$) was found between the ARAT and 9-HPT scores for the more impaired hand. Likewise, a moderate correlation was found between UEFS and the physical health composite scores (PHCSs) of MSQOL-54 ($r_s = -0.59$; $p < 0.001$). Finally, performances on ARAT, 9-HPT, and UEFS differed between the employed individuals and those on long-term disability ($p = 0.007$, $p < 0.001$, and $p = 0.001$). *Conclusion*. The UEFS moderately correlated with the QOL measure, and considering the UESF is a patient-reported outcome, it could be used to complement routinely captured measures of assessing UE function. Further study is warranted to determine which measure, or combination of measures, is more sensitive to changes in UE function over time.

## 1. Introduction

Upper extremity (UE) impairment, caused by a combination of motor and sensory deficits, hinders the ability of individuals with multiple sclerosis (iMS) to perform activities of daily living (ADL) and decreases their quality of life (QOL) [1]. UE impairment is widely reported in iMS affecting proximal and/or distal parts of the upper limbs and is associated with unemployment and negative economic impact [2]. Bertoni et al. studied unilateral and bilateral upper limb dysfunction in 105 iMS and found diminished dexterity, as measured by the Nine-Hole Peg Test (9-HPT), in 75% of their study population [3]. Presently, there are several standardized tools available for clinical assessment of hand dexterity in iMS including the 9-HPT, the box and block test (BBT), and the Jebsen-Taylor Hand Function Test (JTT) [4],

with the 9-HPT most frequently used in clinical practice and research. These commonly used tests do not provide a complete assessment of UE function as each focuses on either proximal arm/hand movements or manual dexterity. The high rate of UE dysfunction in iMS merits careful assessment of the location and type of dysfunction, for example, hand versus shoulder or fine versus gross motor control and any combination therein. Identification of a comprehensive UE outcome measure that could systematically assess more complex and integrated UE function in iMS is needed [4, 5]. Clinicians and researchers require a tool that evaluates all aspects of UE function including manipulation of small and large objects, upper arm movements (reaching, lifting, and transport of objects), and both fine and gross movement components of manual dexterity in iMS, which are indispensable to perform activities of daily living. In a systematic review, Santisteban et al. performed a systematic literature review and found 48 different measures used to report UE function in people with stroke. Both the Action Research Arm Test (ARAT) and the 9-HPT were among the measures used most frequently [6]. The ARAT is found to be extremely useful as a comprehensive and reliable tool evaluating UE function in various studies with stroke patients evaluating UE function across a wide spectrum of impairments [7, 8]. In addition to physical performance tests, the past decade has seen an increase in the use of patient-reported outcome measures (PROMs) for evaluation in clinical settings with few reports on clinical correlation [9]. The Upper Extremity Function Scale (UEFS), which is a PROM, is more likely to detect significant changes as a result of treatment or progression in patients with a variety of UE dysfunctions than traditionally used clinical measures [10]. The multitude of tests available, the increased use of PROM for patient assessment, and the limitations in the 9-HPT bring to question if a more comprehensive measure of assessing UE function, such as the ARAT and UEFS, would better correlate to QOL in iMS. On the basis of these considerations, the objectives of the present study were as follows: (1) to quantitatively assess the relationship between measures of assessing UE function (UEFS, ARAT, and 9-HPT), (2) to understand if the performances on these three measures of assessing UE function correlate with QOL as measured by the Multiple Sclerosis (MS) Quality of Life-54 (MSQOL-54), and (3) to determine differences in the scores obtained from these measures of assessing UE function based on employment status. The primary goal of this study was to evaluate different means of assessing UE function: a PROM: (UEFS) and two physical assessments (ARAT and the 9-HPT) to determine which measure best correlates to QOL as measured by the MSQOL-54. The identified tool(s) can then be used to assess UE function in iMS, monitor for progression, and target appropriate intervention including physical and/or occupational therapy, with the overall objective of improving QOL in iMS.

## 2. Materials and Methods

*2.1. Study Design and Population.* A convenience sample of 112 iMS was prospectively recruited, consented, and evaluated for participation in this descriptive correlational study. Participants were evaluated in one of two locations: 44 participants were recruited at the Saskatchewan MS Connects Conference in November 2018 as a part of an interactive research clinic, and an additional 68 participants were recruited from the Saskatoon MS Clinic at Saskatoon City Hospital. One participant chose not to participate in the 9-HPT and ARAT but completed the UEFS and MSQOL-54; thus, only 111 participants were included in the analysis of the physical assessment measures. Individuals 18 years of age and older who have been physician diagnosed with MS or clinically isolated syndrome were included in this study. Those who were unable to consent for themselves and patients with medical conditions that preclude participation (previous surgery on the upper extremity, any other disorder that affected upper extremity function, serious acute/chronic comorbidities, or neurological disorders other than MS) were excluded from this study. Study data were collected and managed using Research Electronic Data Capture (REDCap), an electronic data capture tool hosted at the University of Saskatchewan. REDCap is a secure web-based platform that is specially designed to support data capture for research purposes [11, 12]. All consent documents, PROMs, and physical performance test data were collected on a tablet using REDCap version 9.3.7. When needed, an investigator assisted the participant with the tablet. Clinical demographic profiles (month and year of birth, sex, year of the first symptom, year of diagnosis, and MS phenotype) were collected from all participants at the time of data collection. Numbers of relapses, expanded disability status scale (EDSS), and employment status were collected from the clinic charts. Information on the current use of MS disease-modifying therapy (DMT) was collected from the participants and clinic charts. Ethics approval for this study was obtained from the University of Saskatchewan's Biomedical Research Ethics Board.

### 2.2. Tools

*2.2.1. Patient-Reported Outcome Measures (PROMs).* The Upper Extremity Functional Scale (UEFS) is an 8-item region-specific questionnaire developed to assess work-related upper extremity disorders. The UEFS is a valid, reliable, and responsive tool designed to measure the impact of upper extremity disorders on function in patients with a variety of diagnoses [10]. It is completed in less than 5 minutes. Participants reported their ability to perform 8 activities (sleeping, writing, opening jars, picking up small objects with fingers, driving a car for more than 30 minutes, carrying a milk jug from the refrigerator, opening a door, and washing dishes) by marking a line on a 0-10 visual analogue scale (VAS) with 0 indicating no problem and 10 indicating a major problem. The total score is calculated by adding VAS scores with possible scores ranging from 0 (best state) to 80 (worst state).

The Multiple Sclerosis Quality of Life-54 (MSQOL-54) is a multidimensional health-related quality of life self-report questionnaire with 11 domains that combine both generic and MS-specific items into a single instrument and can usually be completed with little or no assistance [13]. The

MSQOL-54 demonstrates good internal consistency with high test-retest reliability and construct validity for assessing health-related quality of life in iMS [14, 15]. The 11 domains are physical function, pain, energy, emotional health, role limitations (physical/emotional), health-related perceptions, social function, health-related distress, sexual function, overall quality of life, and cognitive function. Composite scores are calculated for physical health (PHCS) and mental health (MHCS) with higher scores indicating better quality of life.

*2.2.2. Physical Performance Tests.* The Nine-Hole Peg Test (9-HPT) is the most frequently used quantitative measure for upper extremity function, specifically hand dexterity, in MS. The 9-HPT has high interrater reliability, high test-retest reliability, and high discriminative validity [16]. The test is standardized with both hands (dominant and non-dominant) tested twice by timing the participant as they place and then remove 9 pegs on a standardized pegboard. Each trial has a maximum 5-minute (300 second) time limit with 300 seconds recorded if the task could not be completed in the allotted time due to physical limitation. The mean time to complete the task, in seconds, is calculated for each hand [17] with lower scores indicating faster (better) performance. The faster-performing hand was identified as the "less impaired hand"; the other hand was identified as the "more impaired hand." The average of all four trials (both hands were tested twice) was considered as the mean time for both hands.

The Action Research Arm Test (ARAT) is a standardized measure of arm and hand function which consists of 19 items organized in four different sections: grasp, grip, pinch, and gross movement [7]. ARAT was chosen among other upper limb functional measures because it allows a comprehensive evaluation of arm and hand function during the execution of tasks which are quite similar to activities of daily living and could be performed on subjects who are not able to pick up a peg/block. A trained investigator scores each item based on a 4-point ordinal scale, with 0 = unable to perform any part of the relevant task, 1 = able to perform the task partially (e.g. can only lift the relevant object), 2 = able to complete the task; but with abnormally long time/clumsiness/great difficulty, and 3 = able to perform task completely and normally. Participants are first asked to perform the most difficult task within a subscale (grasp/grip/pinch/gross movement). If the participant passes the first task adequately with normal movement, no more tasks in the subscale are administered and all items in the subscale are scored a 3. Likewise, if a participant scores a 0 on the first task within a subscale and scores a 0 on the second task, no more tasks in the subscale are administered and all tasks in the subscale are scored a 0. If the participant scores other than described, all tasks within a subscale are scored. The maximum score for ARAT is 57 for each arm, with a higher score indicating better performance.

*2.3. Statistical Analyses.* Descriptive and inferential statistics were utilized to establish a clinical-demographic profile and relationships between various measures used in this study. The demographic data of our study sample and scores obtained from study measures were expressed as mean ± standard deviation (SD). Spearman's rank correlation coefficient ($r_s$) determined relationships among all PROMs and physical performance tests. Correlations ($r_s$) between 0 and 2.9 (0 and -.29) were interpreted as negligible correlation, 0.3 and 0.49 (-0.3 and -0.49) as low positive (negative) correlation, 0.5 and 0.69 (-0.5 and -0.69) as moderate positive (negative) correlation, 0.7 and 0.89 (-0.7 and -0.89) as high positive (negative) correlation, and 0.9 and 1 (-0.9 and 1) as very high positive (negative) correlation [18, 19]. The Kruskal-Wallis test determined differences in the scores obtained from three measures of assessing UE function (9-HPT, ARAT, and UEFS) stratified by employment status. All statistical analyses were performed using SPSS version 25 with $\alpha = 0.05$ for statistical significance.

## 3. Results

*3.1. Patient Characteristics and Scores Obtained from Study Measures.* 112 iMS (79 female and 33 male mean age 50.3 ± 12.5 years; mean duration of MS 17.1 ± 14.1 years; 71 RRMS, 23 SPMS, 15 PPMS, and 3 CIS) were included in this study. Table 1 shows the clinical-demographic profile of our study population. The median EDSS was 2.75 with 0.41 ± 0.6 (range = 0-3) mean relapses per year. 36 iMS (32.1%) were employed whereas 32 iMS (28.6%) were on long-term disability. 63 iMS (56.3%) were taking MS DMTs. Table 2 describes the mean scores obtained from the measures of assessing UE function and the MSQOL-54. The mean ARAT score (both hands) was 54.1 ± 6.4, the mean 9-HPT score (both hands) was 29.1 ± 23.2 seconds, and the mean UEFS score was 22.4 ± 17.1.

*3.2. Correlations between Various Study Measures.* Figure 1illustrates the correlation between UEFS and PHCS, and ARAT more impaired hand and 9-HPT more impaired hand scores. A moderate negative correlation was found between the UEFS (higher score indicates worse function) and the PHCS (higher score indicates better QOL) ($r_s = -0.59$; $p$ value <0.001). Likewise, a moderate negative correlation was also found between the ARAT (higher scores indicate better function) and 9-HPT scores (higher scores indicate worse function) for the more impaired hand ($r_s = -0.51$; $p$ value <0.001). Table 3 shows the correlations between various upper extremity functional scores (ARAT/9-HPT/UEFS) and MSQOL-54 scores. A low negative correlation was found between the 9-HPT both hands scores (higher score indicates worse function) and the PHCS (higher score indicates better QOL) ($r_s = -0.36$; $p$ value <0.001). Also, a low positive correlation was found between the ARAT both hands score (higher scores indicate better function) and the PHCS (higher score indicates better QOL) ($r_s = 0.33$; $p < 0.001$).

*3.3. Distribution of Upper Extremity Functional Scores according to Employment Status.* The distributions of average ARAT, 9-HPT, and UEFS scores differed between employed individuals and those on long-term disability, with the employed individuals having better scores on the measures of assessing UE function than those on long-

Table 1: Clinical-demographic profile of our study sample.

| Variable | Frequencies (%) $n = 112$ |
|---|---|
| Sex | |
| Females | 79 (70.5%) |
| Males | 33 (29.5%) |
| Mean age (year) | 50.3 ± 12.5 |
| Mean age of onset (year) | 33.1 ± 11.6 |
| Mean duration (year) | 17.1 ± 14.1 |
| MS phenotype | |
| CIS | 3 (2.7%) |
| RRMS | 71 (63.4%) |
| SPMS | 23 (20.5%) |
| PPMS | 15 (13.4%) |
| Mean relapses per year (range) | 0.41 ± 0.6 (0-3) |
| Median EDSS | 2.75 |
| Employment status | |
| Employed | 36 (32.1%) |
| Long-term disability | 32 (28.6%) |
| Retired | 14 (12.5%) |
| Unemployed | 8 (7.1%) |
| Adjusted employment | 2 (1.8%) |
| Self-employed | 5 (4.5%) |
| Unpaid employment | 2 (1.8%) |
| Unknown | 13 (11.6%) |
| MS DMTs | |
| Alemtuzumab | 9 (8.0%) |
| Cladribine | 4 (3.6%) |
| Dimethyl fumarate | 16 (14.3%) |
| Fingolimod | 3 (2.7%) |
| Glatiramer acetate | 9 (8.0%) |
| Interferon beta-1a | 6 (5.4%) |
| Natalizumab | 4 (3.6%) |
| Ocrelizumab | 6 (5.4%) |
| Peginterferon beta-1a | 1 (0.9%) |
| Teriflunomide | 5 (4.5%) |
| None | 49 (43.8%) |

Abbreviations: CIS: clinically isolated syndrome; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; EDSS: expanded disability status scale; MS DMTs: multiple sclerosis specific disease-modifying therapies.

term disability (mean rank scores: ARAT employed = 69.13 and on long − term disability = 41.11, $p = 0.007$; 9-HPT employed = 33.44 and on long − term disability = 74.59, $p < 0.001$; UEFS employed = 39.36 and on long − term disability = 72.39, $p = 0.001$).

## 4. Discussion

UE dysfunction significantly contributes to disability in activities of daily living and could negatively impact QOL in iMS. A comprehensive assessment of UE function may provide additional information on the level of disability and might contribute to better planning of rehabilitation. Our results showed a statistically significant moderate correlation between the UEFS and the MSQOL-54 PHCS. A similar finding was observed by Paltamaa et al. who studied associations among measures of physical functioning and self-reported performance in mobility, domestic life, and self-care in ambulatory iMS. They found manual dexterity was a significant predictor of perceived difficulties in the performance of activities of daily living in ambulatory iMS [20]. Neurologic rating scales, such as the EDSS, are traditionally used to measure clinical disability in MS. However, EDSS has been criticized for lack of sensitivity specifically for evaluation of UE function, its high interrater variability, and its emphasis on ambulation [21, 22]. The Multiple Sclerosis Functional Composite (MSFC), consisting of three quantitative objective assessments to detect changes in ambulation, UE function, and cognition, was developed to address these limitations [23]. The 9-HPT, a component of MSFC, is now a frequently used measure to detect a change in UE function in iMS both in clinical practice and research [16]. However, the disadvantage of 9-HPT is its inability to detect proximal weakness, and it may not be useful in detecting UE impairment or progression of impairment in iMS who cannot pick up the pegs used in the 9-HPT.

Preservation of UE function in iMS is considered a potential treatment benefit. In individuals with restricted walking ability, maintaining UE function is of paramount importance as this could affect a person's ability to use walking aids [24]. The severity of UE impairment in iMS was suggested in a study in which 51% of the study sample ($n = 285$) reported at least moderate difficulty in hand

Table 2: Mean scores of measures of assessing upper extremity function and MSQOL-54.

| |
|---|
| ARAT scores mean ± SD ($n = 111^*$) |
| Both hands = 54.1 ± 6.4 |
| Dominant hand = 54.6 ± 5.6 |
| Nondominant hand = 53.6 ± 8.2 |
| Less impaired hand = 55.0 ± 5.3 |
| More impaired hand = 53.2 ± 8.3 |
| 9-HPT scores mean ± SD ($n = 111^*$) |
| Both hands = 29.1 ± 23.2 |
| Dominant hand = 25.2 ± 8.9 |
| Nondominant hand = 33.0 ± 41.8 |
| Less impaired hand = 23.8 ± 6.8 |
| More impaired hand = 34.4 ± 41.9 |
| UEFS score mean ± SD($n = 112$) = 22.4 ± 17.1 |
| MSQOl-54 scores mean ± SD ($n = 112$) |
| PHCS = 57.7 ± 19.4; MHCS = 65.1 ± 22.1 |

*One participant chose not to participate in the 9-HPT and ARAT but completed the UEFS and MSQOL-54. Abbreviations: ARAT: Action Research Arm Test; 9-HPT: Nine-Hole Peg Test; UEFS: Upper Extremity Function Scale; MSQOL-54: Multiple Sclerosis Quality of Life-54; PHCS: physical health composite score; MHCS: mental health composite score; SD: standard deviation.

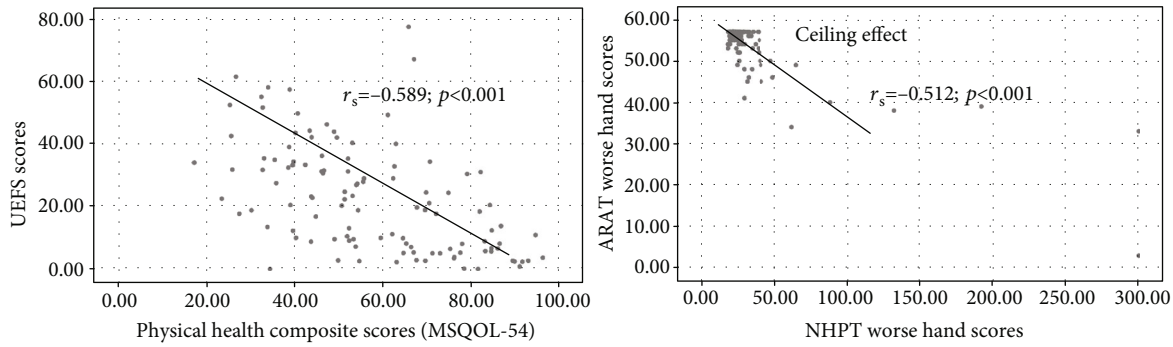


Figure 1: Correlation between study measures.

Table 3: Correlations between various measures of assessing upper extremity function (ARAT/9-HPT/UEFS) and MSQOL-54 scores.

| Scores | 9-HPT dominant hand score | 9-HPT nondominant hand score | 9-HPT less impaired hand score | 9-HPT more impaired hand score | 9-HPT both hands score | UEFS score | PHCS | MHCS |
|---|---|---|---|---|---|---|---|---|
| ARAT dominant hand score | -0.403; $p < 0.001^*$ | -0.350; $p < 0.001^*$ | -0.379; $p < 0.001^*$ | -0.395; $p < 0.001^*$ | -0.410; $p < 0.001^*$ | -0.333; $p < 0.001^*$ | 0.243; $p = 0.010^*$ | 0.072; $p = 0.452$ |
| ARAT nondominant hand score | -0.303; $p = 0.001^*$ | -0.396; $p < 0.001^*$ | -0.312; $p = 0.001^*$ | -0.400; $p < 0.001^*$ | -0.389; $p < 0.001^*$ | -0.349; $p < 0.001^*$ | 0.291; $p = 0.002^*$ | 0.185; $p = 0.052$ |
| ARAT less impaired hand score | -0.255; $p = 0.007^*$ | -0.275; $p = 0.004^*$ | -0.258; $p = 0.007^*$ | -0.283; $p = 0.003^*$ | -0.285; $p = 0.003^*$ | -0.393; $p < 0.001^*$ | 0.245; $p = 0.010^*$ | 0.146; $p = 0.125$ |
| ARAT more impaired hand score | -0.445; $p < 0.001^*$ | -0.473; $p < 0.001^*$ | -0.429; $p < 0.001^*$ | -0.512; $p < 0.001^*$ | -0.51; $p < 0.001^*$ | -0.31; $p = 0.001^*$ | 0.295; $p = 0.002^*$ | 0.122; $p = 0.201$ |
| ARAT both hands score | -0.405; $p < 0.001^*$ | -0.445; $p < 0.001^*$ | -0.398; $p < 0.001^*$ | -0.474; $p < 0.001^*$ | -0.471; $p = <0.001^*$ | -0.371; $p < 0.001^*$ | 0.327; $p < 0.001^*$ | 0.169; $p = 0.077$ |
| UEFS score | 0.355; $p < 0.001^*$ | 0.333; $p < 0.001^*$ | 0.331; $p < 0.001^*$ | 0.364; $p < 0.001^*$ | 0.354; $p < 0.001^*$ | N/A | -0.589; $p < 0.001^*$ | -0.406; $p < 0.001^*$ |
| PHCS | -0.370; $p < 0.001^*$ | -0.336; $p < 0.001^*$ | -0.387; $p < 0.001^*$ | -0.326; $p < 0.001^*$ | -0.358; $p < 0.001^*$ | -0.589; $p < 0.001^*$ | N/A | 0.710; $p < 0.001^*$ |
| MHCS | -0.210; $p = 0.027^*$ | -0.141; $p = 0.139^*$ | -0.216; $p = 0.023^*$ | -0.128; $p = 0.180$ | -0.165; $p = 0.083$ | -0.406; $p < 0.001^*$ | 0.710; $p < 0.001^*$ | N/A |

$^*p$ value is significant at $\alpha = 0.05$. Note: negligible to low correlations were found between the scores obtained from objective measures of assessing UE function (ARAT and 9-HPT) and PHCS of MSQOL-54. Abbreviations: ARAT: Action Research Arm Test; 9-HPT: Nine-Hole Peg Test; UEFS: Upper Extremity Function Scale; MSQOL-54: Multiple Sclerosis Quality of Life-54; PHCS: physical health composite score; MHCS: mental health composite score; N/A: not applicable.

function [25]. We found performance on the three UE function measures differed between employed iMS and those who were on long-term disability, with employed individuals had better mean rank scores on all three measures than those on long-term disability. This finding is in line with a study conducted by Marrie et al. who found an association of UE dysfunction with decreased odds of being employed (OR 0.97; 95% CI: 0.96, 0.98) and showed currently employed iMS had higher UE function scores than unemployed patients [2]. However, it is often difficult to ascertain and measure the variety of functional domains leading to UE impairments in iMS. Therefore, there remains a need for a measure of assessing UE function that could adequately capture UE impairments in individuals with greater levels of disability and measure peoples' ability to perform routine tasks in daily life. The ARAT, with its subscales for grasp, grip, pinch, and gross movements, could provide a more comprehensive functional assessment in iMS, and the UEFS might be valuable in providing the patient's perspective on the magnitude of UE dysfunction.

PROMs are increasingly being recommended for use as integral components in clinical trials [26]. Our analyses indicate UEFS (PROM) scores had weak correlations with performance on the ARAT and the 9-HPT. These findings align with those of Feys et al. who studied 43 iMS with upper limb dysfunction and found a poor to moderate correlation of upper extremity performance-based measures (TEMPA, Jebsen Hand Function Test, and 9-HPT) with an ADL self-questionnaire [27]. These poor correlations between self-reported and objective measures may be due

to an individuals' ability to adapt to impairment. However, PROMs provide the patient's perspective and could complement objective assessments by identifying outcomes not routinely captured during clinical assessment. We found a statistically significant moderate correlation between UEFS and the physical health composite scores of MSQOL-54. Such outcome measures provide additional information on the daily life difficulties experienced by iMS, and improvement in these performance measures is being considered as the ultimate goal of any treatment or rehabilitative strategies.

A limitation of this study is that our convenience sample was skewed to iMS with mild disability (median EDSS = 2.75) with few limitations in arm/hand strength and gross movements. Thus, a future study should include more individuals with higher levels of disability as measured by the EDSS scores and progressive forms of MS. Our analysis of the scatter plot indicates that the ARAT had a ceiling effect (when a high proportion of study participants (>20%) have the highest possible score [28]). This is in line with a previous study conducted by Lamers et al. to determine the relationship between clinical tests in MS and real-life arm performance involving 30 iMS and 30 healthy controls. They also found a ceiling effect in the ARAT for the dominant arm [29]. Recently, Solaro et al. reported a floor and ceiling effect for the 9-HPT in iMS with mild (EDSS < 3) and severe (EDSS > 6) disease, respectively. They also found individuals with PPMS have more hand asymmetry as measured by the 9-HPT [30]. However, these preliminary findings require further investigation to draw any firm conclusions on floor and ceiling effects. Another limitation is that majority of our study participants were recruited from a single MS center, and therefore, caution should be taken with the generalization of our study results. We also do not have longitudinal data on the outcome measures which could have provided additional information. A further limitation of this study is that descriptors of disease activity in terms of relapse and/or active lesions on brain/spinal cord magnetic resonance imaging scans were not addressed in the eligibility criteria. Future studies could be designed to compare upper extremity function in patients with active disease versus nonactive disease.

The selection of a relevant measure of assessing UE function depends on the intended purpose of evaluation and severity of UE dysfunction. While the 9-HPT is an objective measure of assessing UE function, it does not measure peoples' ability to perform routine tasks in daily life, and it focuses on finger dexterity and may not be useful in iMS who cannot pick up the pegs utilized in the 9-HPT. Recently, a few studies [29, 31] have shown that although scores on objective measures of UE function are within normal range, iMS still report UE disability affecting their performance on activities of daily living. Therefore, it would be ideal to comprehensively evaluate UE function using both subjective and objective measures of assessing to better understand UE disability in iMS. Our results suggest that the performance on the UEFS moderately correlates with the QOL measure, and therefore, it could be instrumental in providing additional information on the difficulties experienced by iMS when performing specific UE tasks.

## 5. Conclusions

The performance on UEFS significantly correlated with the quality of life measure, and therefore, it could complement routinely captured measures of assessing UE function in iMS. Further study is warranted to determine which test, or combination of tests, is more sensitive to changes in UE function in iMS over time. Such measurements of UE function may provide additional information on disability accrual and could enhance the planning of rehabilitation programs targeted to improve the quality of life in iMS.

## Abbreviations

| | |
|---|---|
| UEFS: | Upper Extremity Function Scale |
| MSQOL-54: | Multiple Sclerosis Quality of Life-54 |
| 9-HPT: | Nine-Hole Peg Test |
| ARAT: | Action Research Arm Test |
| $r_s$: | Spearman's correlation coefficient |
| QOL: | Quality of life |
| UE: | Upper extremity |
| ADL: | Activities of daily living |
| iMS: | Individuals with multiple sclerosis |
| PROM: | Patient-reported outcome measure |
| EDSS: | Expanded disability status scale |
| DMT: | Disease-modifying therapy. |

## Data Availability

The data used to support the findings of this study have not been made available because we do not have ethical permission to share or release any primary research data.

## Ethical Approval

The method of our longitudinal study (observational in nature) was approved by the University of Saskatchewan's Biomedical Research Ethics Board with the reference number "Protocol BIO 484."

## Conflicts of Interest

Dr. Levin has received educational and/or consulting funding from Biogen Idec, Pendopharm, and Sanofi Genzyme. Dr. Zucker-Levin, Dr. Saini, Dr. Donkers, Benjamin McMillan, and Pawan Kumar have no conflicts of interest.

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