Title: Safety and effectiveness of the Walk 'n Watch structured, progressive exercise protocol delivered by physical therapists for inpatient stroke rehabilitation in Canada: a phase 3, multisite, pragmatic, stepped-wedge, cluster-randomised controlled trial

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ABSTRACT

Background

Though clinical guidelines support high repetitions of walking after stroke, practice is slow to change. We undertook an implementation trial to enable entire stroke units to use the Walk ‘n Watch (WnW) structured, progressive exercise protocol. Our objective was to evaluate the impact of the WnW implementation package on stroke patient outcomes of the primary endpoint of walking endurance (6MWT), and secondary outcomes, including balance, mobility, depression, disability, quality of life, cardiovascular outcomes and global cognition measures after 4 weeks in an inpatient stroke rehabilitation setting.

Methods

This pragmatic Phase 3, 12-site clinical trial across seven Canadian provinces used a stepped-wedge cluster design to randomize when sites (inpatient stroke rehabilitation units) changed practice from Usual Care to WnW. Each site was randomly allocated to one of four transition sequences with three sites in each sequence. All front-line Physical Therapists were trained. WnW required completion of a minimum of 30 minutes of daily walking-related activities that progressively increased in intensity based on heart rate and step count monitors. Progressions were prescribed based on a screening 6MWT done by the front-line Physical Therapist as part of the protocol. Blinded assessors completed evaluations at baseline and four weeks later. Primary analysis used a linear mixed-effects model adjusted for unit size, stratum, calendar time, age, sex, and baseline 6MWT.

Findings

The trial enrolled 12 sites with 314 participants, eight were deemed ineligible after enrolment, and 306 were included in the primary analysis (162 Usual Care, 144 WnW) with a mean(SD) age

of 68(13) years, 29(17) days since stroke, and a baseline 6MWT of 152(106)m. Usual Care 6MWT was 137.1(100.9)m at baseline and 223.6(130.4)m after 4 weeks. WnW 6MWT was 163.6(112.7)m at baseline and 297.2(133.2)m at 4 weeks. The 6MWT improvement was 44m(95%CI 12·7,76·1) greater for WnW compared to Usual Care. Further, WnW improved quality of life, balance, and gait speed. No serious adverse events occurred during a WnW session.

Interpretation

WnW improved walking with clinically meaningful changes in subacute stroke within a real-world setting where 85 therapists delivered the intervention across 12 sites as part of usual care. The WnW protocol, consisting of structured progressions based on a screening 6MWT, can be readily implemented into practice today with minimal additional resources. The protocol can be readily implemented into practice with minimal additional resources. Further research is needed to identify characteristics of patients that benefit the most from WnW.

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INTRODUCTION

Annually, there are 12 million new stroke cases worldwide making stroke one of the leading causes of global disability.[1] Regaining walking independence is one of the top priorities listed by people living with stroke, their caregivers, and health professionals.[2] Clinical practice guidelines support high repetitions of walking practice to achieve independence in walking after stroke.[3] Yet, practice is slow to change with low levels of walking activity in stroke rehabilitation units,[4,5] despite the greatest potential for neuroplasticity within the first few months post-stroke.[6]

Animal models and human mechanistic studies demonstrate that structured, progressive exercise, once the patient is medically stable, can harness the greater neuroplasticity present in the first few months after a stroke.[6] There are Phase 3 trials that have tested whether increased exercise intensity during inpatient stroke rehabilitation can improve walking (e.g., LEAPS[7] and PHYS-STROKE[8] trials had a primary outcome of gait speed). However, the number of these trials that are pragmatic are few. Pragmatic trials that test the effectiveness of an innovation under usual care conditions, make up less than 5% of clinical trials;[9] such designs improve the applicability of the findings and facilitate uptake. The pragmatic FIT-Stroke (n=250 patients involving 60 therapists) found an outpatient circuit training program resulted in a 20m between-group difference in the 6MWT compared to usual care.[10] The CIRCIT trial (n=283 patients involving unit physiotherapists, therapy assistants and students) found no between-group differences after 4 weeks of 5-day/week standard of care inpatient stroke physiotherapy versus 7-day/week physiotherapy or a group circuit class 5-day/week[11]. The MOBILISE trial (n=126 non-ambulatory patients involving 25 therapists) found that treadmill walking with body weight support resulted in a non-significant increase in the number of people walking independently after stroke [12] A Phase 3 study implemented into usual inpatient stroke rehabilitation practice

(SIRRACT Trial, n=135) found no improvement in walking speed with thrice weekly feedback and encouragement based on step-count sensor data (daily walking steps, distance and speed) versus feedback on the 10-meter walk distance.[13]

In our recent RCT, one experienced, trained research therapist (plus a backfill therapist) per site delivered our structured, progressive protocol integrated into daily inpatient physical therapy.[14] The protocol resulted in substantially greater walking activity during therapy and improved walking (60m on a 6-Minute Walk Test; 6MWT) and quality of life measures over usual care after 4 weeks of inpatient rehabilitation.[14] Many barriers to implementing higher intensity protocols exist early after stroke.[15] An intervention that is effective in real-world settings will have widespread generalizability for stroke units, providers who deliver the intervention, and patients who receive the intervention. Thus, we undertook a pragmatic implementation trial to change routine practice using a stepped-wedge cluster randomized design to control when stroke units (randomized into sequences) were exposed to the intervention. Our objective was to evaluate the impact of the Walk ‘n Watch (WnW) implementation package on stroke patient outcomes of the primary endpoint of walking endurance (6MWT), and secondary outcomes, including balance, mobility, depression, disability, quality of life, cardiovascular outcomes and global cognition measures after 4 weeks in an inpatient stroke rehabilitation setting.

METHODS

Trial Design

Trial design and protocol have been previously described (www.ClinicalTrials.gov ID: NCT04238260).[16] The trial meets the criteria for a pragmatic trial given its focus on delivering the intervention in routine clinical practice involving staff with typical experience levels and resources,[17] and is a Phase 3 trial as defined by the National Institutes of Health.[18] This study

followed the Consolidated Standards of Reporting Trials (CONSORT) extension for the stepped-wedge cluster randomized trial reporting guideline.[19] (Supplementary Material, page S25) Briefly, we used a stepped-wedge cluster design to randomize when each site transitioned from Usual Care to the WnW protocol; thus participants were assessed in either Usual Care or WnW intervention periods. The trial protocol was approved by the local institutional review boards of: University of British Columbia Clinical Research Ethics Board (H19-02809); Bruyère Health Research Ethics Board (M16-20-015); Research Ethics Board at Centre intégrés universitaire de santé et de services sociaux (MP-13-2020-1947); Research Ethics Board at Centre ntégrés universitaire de santé et de services sociaux de l'Estrie - Centre hospitalier universitaire de Sherbrooke (MEO-13-2022-458); Horizon Health Network Research Ethics Board (#100731); Waterloo-Wellington Research Ethics Board (#2021-0741); University of Alberta Health Research Ethics Board (Pro00097418); Joseph Brant Hospital Research Ethics Committee (#000-053-20); Prince Edward Island Research Ethics Board; and University of Saskatchewan Biomedical Research Ethics Board (#1673). A Data Safety and Monitoring Board (DSMB) has been established to monitor adverse events. The DSMB has three members with expertise in clinical trials, statistics, and stroke rehabilitation. Serious adverse events (SAEs) related to study participation were summarised and reported to the DSMB and relevant institutional review boards within 48 hours. There were no changes to methods or outcomes after trial commencement.

Population

The intervention was delivered at 12 Canadian hospital sites across seven provinces that provided inpatient stroke rehabilitation services. Sites were chosen to reflect both urban and rural populations across Canada. Consecutive patients were screened and enrolled and were

eligible if they were medically stable adults with a confirmed stroke within 12 weeks, able to understand and follow instructions, had walking rehabilitation goals, and able to walk 5 steps with a maximum of one person helping. Key exclusion criteria were diagnosis of other neurological conditions, enrolment in another rehabilitation trial, or expected to receive less than 2 weeks of rehabilitation. Full inclusion/exclusion criteria are in the Supplementary Material, page S7.

Randomization

Hospital site was the cluster unit of randomization. Computerized randomization was completed by the trial statistician (HW, unaffiliated with any site) prior to trial commencement with each site randomly allocated to one of four transition sequences, and three sites allocated to each sequence. The sequences were 4, 8, 12, or 16 months of Usual Care, followed by a 2-week transition period, with the remaining portion of the 20-month enrollment period designated as the WnW intervention (Supplementary Figure S1, page S20). Randomizations were stratified within two unit-size strata with the four largest sites (based on expected enrollment) in stratum one and the eight remaining in stratum two. Sites were notified of their own transition date after they recruited their first participant and were not informed of the other sites' transition dates. Patients who met eligibility in either Usual Care or WnW were consented by site study coordinators and provided written informed consent to enable their collection of outcome measures. Additional consent for receiving the WnW intervention was not required, as this protocol was considered an improved form of Usual Care (e.g., structured, progressive exercise). Patient flow procedures for Usual Care and WnW are illustrated in Figure S2 and S3 (Supplementary Material, page S21–22).

Usual Care

Physical therapists delivered care to patients with no changes made to therapy. Physical therapy usual care in Canada typically consists of 5 days/week of 30-60 minutes of physical therapy with some sites utilizing rehabilitation assistant(s) to deliver aspects of treatment.

Minimizing Contamination and Transition Period

We took a number of steps to minimize contamination. During the Phase 1 Usual Care phase, sites had no communication with any other sites, and were not informed of the other sites participating. All resources (e.g., website) were password protected and only provided once the site switched into the WnW phase. Further, a 2-week transition period was incorporated to enable therapists to complete Phase 1 Usual Care patients before starting Phase 2 WnW patients.

During this transition period, recruitment was paused for 2 weeks. During this pause, we rolled out the implementation package (outlined in Table 1) at the site level, and therapists then delivered the intervention to their individual patients. The implementation package included training all front-line physical therapists and rehabilitation assistants on the unit through online training workshops with hands-on practice (two 2-hour sessions), manuals, and videos (www.neurorehab.med.ubc.ca). Each site was provided onboarding materials to address staff changes so therapists who did not attend the initial training could adopt the protocol. Further, each site identified a 'protocol champion' to facilitate initial weekly huddles with therapists to discuss barriers to implementation. Front-line therapists were trained to complete safety screening, determine eligibility, and complete the protocol as an improved form of Usual Care with all patients who met eligibility criteria - not just those who consented to outcome measures.

WnW Implementation

The amount of physical therapy (minutes and sessions) varied between sites, but was the same for each site between Usual Care and WnW (typically 5 days/week of 30-60 minutes of one-on-

one physical therapy). The steps for WnW (checking eligibility, screening and delivery of intervention) are detailed in Figure 1. Therapists initiated WnW for each patient admitted to the unit who met eligibility criteria, cleared the safety screen and then delivered WnW 5 days/week for at least 4 weeks or until the patient was discharged from their hospital unit. Step-targets were individualized based on initial performance on the 6-Minute Walk Test (6MWT), with targets identified for the end of week 1, 2, and 4 (Figure 1). These targets were calculated based on data from our original RCT.[14,20] Therapists were provided numerous examples and case studies of WnW implementation and used their clinical judgement on how to achieve protocol targets. A key goal was to increase the number of steps completed within 30 minutes with a target heart rate of 40 to 60% heart rate reserve[16] informed by a watch measuring heart rate (Garmin Forerunner 235 or 735XT, Garmin Ltd., USA) and step counter (Fitbit Inspire, Alphabet Inc., USA, placed on the ankle)[21] during physical therapy sessions. Assistive devices (e.g., canes, walkers and ankle foot orthoses) were used at the discretion of the therapists for both Usual Care and WnW.

Trial outcomes

The primary outcome was the change in distance walked on the 6MWT from baseline to 4 weeks at the individual patient level. The 6MWT is a valid and reliable measure to assess walking endurance and recovery early after stroke.[22] Secondary outcomes were resting blood pressure, heart rate, quality of life (EQ5D), global cognition (Montreal Cognitive Assessment–MoCA), balance and mobility (Short Physical Performance Battery–SPPB), depression (Patient Health Questionnaire–PHQ-9), and disability (Modified Rankin Scale–mRS). Gait speed from the SPPB walking item (4 metres at usual pace) was also calculated. A retention measurement was undertaken at 12-months post-stroke and these results will be reported in a future publication.

Blinding and assessment schedule

Blinded assessors completed the primary and secondary outcomes at baseline and 4 weeks later, which is typically near discharge in Canadian inpatient stroke rehabilitation units. Assessors were not involved in the stroke rehabilitation unit or with delivering the protocol, naive to the WnW intervention, and unaware of whether participants received Usual Care or WnW. Participants were informed they were receiving usual care in each phase of the trial as the WnW became Usual Care during that phase of the trial. As a result, participants were blinded to the transition from Usual Care to WnW. Study fidelity was assessed at two weeks after the baseline outcomes for both the Usual Care and WnW group, where one session of physical therapy was measured with step counters (StepWatch™ (Modus Health, USA)).[21]

Statistical analysis

The power calculations were performed using the R package, swCRTdesign. The input values were derived from a mixed-effects model analysis of the pilot trial data, in which the treatment effect was a 60-meter improvement in the 6MWT, and the effective (adjusted for covariates including baseline 6MWT) within group standard deviation was 90 meters based on previous trial results.[14] The intra-cluster correlation coefficient (ICC) was essentially zero, but we used a value of 0.01 in the power calculation to be conservative. Based on these input values and an assumed cluster auto-correlation coefficient (CAC) of 0.8, a design with a total of 12 sites, and 3 clusters transitioning at each step, requires 13 participants per cluster, or 156 participants in total, to achieve 80% power with a Type I error rate of 5%. Note that this calculation is insensitive to the assumed CAC value due to the low ICC value. Allowing for 20% dropout increases the sample size to 195.

Descriptive statistics were summarized with means and SD for continuous variables and with percentages and counts for categorical variables. The primary intent-to-treat analysis used a

linear mixed-effects model to compare the improvement in 6MWT from baseline to 4 weeks between WnW versus Usual Care at the individual patient level. The model included a random intercept to account for clustering within sites, and adjusted for unit size stratum, calendar time (measured as years since the start of the study to the date of consent to capture a potential time trend), age, sex (self-report), and baseline 6MWT to account for baseline differences (Supplementary Material, page S6). The covariates were pre-specified and included either because they were utilized in the randomization design (e.g. stratum, and clustering by site) or they were potentially strong predictors of the outcome so that their inclusion could mitigate bias due to chance imbalance as well as increase precision of the intervention effect estimate. Higher age and female sex have been previously associated with poorer outcomes after stroke.[23] As a sensitivity analyses, we used multiple imputation to fill in missing 4-week 6MWT scores and fit the linear mixed effect model to the completed datasets. Participant's treatment group, age, sex, calendar time, stratum and primary and secondary outcomes measured at baseline which might be related to data missingness were used in the multiple imputation model. Secondary outcomes were analyzed using analogous linear (or logistic, for the dichotomized mRS outcome) mixed effects models.

To assess the impact of intervention fidelity on the primary outcome, we conducted a per protocol analysis which included only sites that met at least 50% of the step target, averaged across participants, on the 2-week fidelity measure. All analyses were conducted using R Statistical Software (version 4.2.2).

No funders contributed to any aspect of the study.

RESULTS

Study Enrollment

Enrollment began in June 4 2021 and ended in February 25 2024 (Supplementary Table S1, page S23). All 12 sites adhered to the transition sequence to which they were randomized and were included in the intent-to-treat analyses (i.e., 12 sites in the Usual Care and the same 12 sites in the WnW). However, the time periods of when each site delivered Usual Care and WnW varied from the planned schedule (Supplementary Table S1, page S23) due to logistical constraints related to the COVID-19 pandemic or availability of staff for the initial training. As the stepped-wedge design requires recruitment over predetermined time windows (rather than stopping at a fixed sample), we recruited more participants than our original sample size estimations which were conservatively calculated. Details of the number of patients screened and enrolled are shown in the CONSORT diagram (Table 2). We enrolled 306 participants, with 162 participants in Usual Care and 144 in WnW. Across all sites, 85 physical therapists and rehabilitation assistants were involved with delivering treatment to patients across the WnW trial period.

Participant characteristics

Baseline characteristics are in Table 3. Participants were 68 years (SD13) old and 29 days (SD17) since stroke with 188(61·4%) males and 118(38·6%) females. At baseline, as a group, the 6MWT was 152m (SD106) indicating participants were severely impaired in walking endurance compared with age-matched adults at least 60 years old (norms of 499m, 95% CI 480-519).[23] The arms were well-balanced with respect to patient characteristics.

Intervention Retention and Fidelity

The retention of participants was high with 92% (n=149/162) of Usual Care participants completing the 4-week assessment and 92% (133/144) of the WnW completing the 4-week assessment. Two weeks after the baseline outcomes, one session of physical therapy was measured with step counters as an indicator of treatment intensity for both groups, as well as an

indicator of fidelity for WnW. Usual Care steps for this single session was 980·0, SD 577·4 while WnW steps were 1513·4, SD 826·7. Treatment intensity was also quantified by the percent of participants who attained at least 1500 steps if their baseline 6MWT was 100 m or less; 2500 steps if their baseline 6MWT was 101-200 m; and 3500 steps if their baseline 6MWT was more than 200 m. These thresholds were based on prior work for walking steps in a physical therapy session measured at 2 weeks post-admission that resulted in improved outcomes, and were also the 2-week step targets for WnW.[20] Participants in Usual Care reached 42·1% (range 0 to 100%, SD 21·5%) of these thresholds based on starting 6MWT distance. Participants in WnW achieved 61·7% of these thresholds (range 7 to 130%, SD 25·7%). Three of the 12 sites (n=74) did not meet 50% of the thresholds, averaged across participants, on the 2-week measure and were removed for the per protocol analyses.

Trial Outcomes

Mean outcomes at baseline and at time-trend-adjusted mean outcomes at 4 weeks are shown in Table 4 and Table S2 (Supplementary Material, page S24). In the intent-to-treat analysis, the improvement on the 6MWT was 43·6m (95% CI [12·7, 76·1]) greater in the WnW group compared to the Usual Care group (Table 5). The intra-cluster correlation coefficient for the 6MWT was 0.035 (95% CI [0·00, 0·12]). The estimated improvement in the multiple-imputation sensitivity analysis was 39·7m (95% CI [6·9, 72·5]). The amount of missing data was similar in the Usual Care and Walk N Watch (7-10%) (Supplementary Table S4, page S24). In subgroup analyses by sex, the improvement on the 6MWT was 64.1m (95% CI [28·3, 99·9]) for males, but only 15·7m (95% CI [-23·3, 54·7] for females. The benefit of WnW on the improvement on the 6MWT was similar across age groups. For secondary outcomes, improvement was greater in the WnW group for quality of life (EQ5D VAS), balance and mobility (SPPB), and gait speed over

Usual Care. In the per protocol analyses with 9 of the 12 sites, there were further benefits of the protocol with a 52.6 m 95% CI [16·3, 89·4] greater improvement in the WnW group compared to the Usual Care group (Table 5).

Safety

Nine SAEs were reported and required admission to acute care. Four SAEs for the Usual Care group were increased vertigo and diaphoresis during their physical therapy walking rehabilitation, bladder complication, suspected seizure with fall in washroom and suspected recurrent stroke while on home visit. Five SAEs for the WnW group were suspected arrhythmias while on the rehabilitation unit, a pseudoaneurysm, severe COVID, suspected recurrent stroke (had not started WnW), and aspiration pneumonia. These events were detected while the participants were on the ward and no SAEs occurred during a WnW session. The case with COVID resulted in death.

Falls were recorded over 4 weeks from rehabilitation admission. Twenty-nine falls were reported from 22 participants in the Usual Care group and 29 falls from 24 participants in the WnW group. Of all 58 falls, only one occurred during a WnW session; the participant lost their balance while stepping onto the stairs and experienced one minor fall. No injuries were sustained. The remaining 57 did not occur during physical therapy, although one fall occurred during an occupational therapy session. Many of the falls (25) occurred in the participant's hospital room (13) or washroom (14).

DISCUSSION

Enabled by implementation strategies, WnW is the one of the first pragmatic Phase 3 trials to test the effectiveness of structured, progressive exercise within a real-world setting. The protocol was effective in increasing the step count during a physical therapy session by 55% (from 974 to

1513 steps) when measured at the 2-week midpoint session, and this translated into walking improvements. For our primary outcome, the minimum clinically important difference (MCID) for the 6MWT ranges from 14m to 30·5m across multiple patient groups.[24] In sub-acute stroke, MCIDs vary from 20m[25] to 71m.[26] We observed a 44m improvement (53m per protocol) in people who received WnW, which falls within the range of MCIDs reported previously.[23–26] An improvement of 40 m on the 6MWT has been associated with improvements in aerobic capacity with a moderate effect size (measured by cardiopulmonary exercise testing) in cardiovascular populations.[27] For secondary outcomes, the WnW group improved in quality of life, mobility, and gait speed compared to Usual care, and were mostly within the MCID. The MCID of the SPPB in patients with heart pathology is at least 1 point,[28] while a small meaningful change of 0·27 to 0·55 has been reported in subacute stroke.[25] This suggests that the WnW group achieved a clinically meaningful improvement in mobility with a 1·11 change in SPPB. A one point increase in SPPB is associated with a 15% lower odds of falling in older adults.[29] Our EQ5D VAS change of 7·99 was higher than the MCID of 6·4 reported in a systematic review of 25 studies involving non-musculoskeletal chronic health conditions,[30] but slightly less than the MCID range for chronic stroke (8·61 to 10·82).[31] A systematic review on the MCID of gait speed in patients with pathology, including stroke, reported changes of 0·10 to 0·20 m/s.[32] Our observed improvement of 0·13 m/s falls in the lower window of this change. The mRS represents a measure of global disability and is widely used as an endpoint in acute stroke trials, but less so with rehabilitation trials. Although the uncertainty on the odds ratio for a favourable mRS outcome precludes definitive conclusions, the large magnitude (1.73) of the odds ratio was notable. We observed that 49% of participants shifted to a favourable outcome (mRS ≤2) in the Walk ‘n Watch group, compared to 33% of participants in usual care.

371 The between-group improvement of 44m in the 6MWT was slightly less than the 60m change
372 found in our earlier RCT,[13] but better adherence to the protocol did improve the outcomes as
373 demonstrated by a 53m improvement in the per protocol analysis. In our earlier trial, participants
374 were younger (mean 57 years) while our current trial matched the typical age for stroke (68(13)
375 years); functional recovery is known to be less in older adults. The pragmatic design also likely
376 contributed to these differences. In contrast to our original trial where one experienced therapist
377 delivered the intervention per site,[14] all front-line therapists were trained to complete the
378 protocol, including eligibility, safety screening, and executing the protocol, regardless of whether
379 the patient consented to the study outcome measures. The large number of therapists (85 across
380 12 sites) that delivered the protocol ranged in staffing experience. Sites were responsible for
381 managing the training of new staff due to staffing changes over time which may have added
382 variability in protocol fidelity. Further, in our original trial, sites were primarily urban, teaching
383 hospitals that typically had 1-hour daily sessions dedicated to physical therapy. Under real world
384 conditions, our sites typically had 30–45-minute sessions with only a few sites with 1-hour
385 sessions. Despite these differences, improvements in the 6MWT indicate that WnW is robust to
386 real world conditions.

387 The greater recovery of walking and balance achieved through WnW without any increase in
388 adverse events has substantial implications on common secondary complications that occur after
389 stroke. Improving walking and balance reduces the risk for falls after stroke while enabling
390 walking physical activity can reduce the risk of future vascular events after stroke.[33] The protocol
391 was successfully applied across a range of abilities in an older adult population with a mean age
392 of 68 which is typical for stroke; some patients could take just a few steps with one-person
393 assistance while patients with the least impairment were walking 300 to 400 metres within six

minutes which is indicative of community-level mobility. The intervention required the therapists to complete a 6MWT as part of the screening process which was instrumental as a basis for setting the step targets that enabled the protocol to accommodate different walking levels. Although not part of the protocol, one site was able to add steps per physical therapy session into their electronic health records system to facilitate documentation and progressions.

The sample comprised 40% women, which is consistent with female participation in rehabilitation studies.[34] Women tend to be older at the time of their stroke and have poorer outcomes,[35] and hence, a lower proportion of women are admitted for inpatient rehabilitation.[36] The benefit of WnW appears greater in men than women. A Canadian study followed over 20,000 stroke patients during inpatient rehabilitation and did not find any meaningful sex differences in outcomes.[36] While a difference in benefit appears to exist, future analyses will model characteristics that might vary between men and women (e.g., baseline walking endurance or depression). Furthermore, ways to better customize the protocol to benefit women should be explored.

There are limitations to this study. Some of the data collection period occurred during the COVID-19 pandemic which resulted in intermittent inability to recruit participants or collect outcome measures. The observed ICC for the 6MWT was larger than what was seen in the pilot study, but the wide 95% confidence interval of the ICC suggests the difference may simply reflect sampling variability. But it is also possible that this larger ICC was due to more heterogeneity in the type of sites recruiting to this trial.

CONCLUSION

The implementation trial design enabled the protocol to be tested under real-world conditions, involving all therapists on each unit for protocol delivery. This pragmatic trial resulted in

clinically meaningful improvements in walking, balance and quality of life in participants with subacute stroke. Better adherence to the protocol resulted in greater treatment benefits. The WnW protocol, consisting of structured progressions based on a screening 6MWT, can be readily implemented into practice today with minimal additional resources. Further research is needed to identify characteristics of patients that benefit the most from WnW.

Table 1. CONSORT Diagram for the Primary Outcome (6MWT at 4-weeks)

		Period 1	Period 2	Period 3	Period 4	Period 5	Totals from Periods 1 to 5	
							Phase 1 (Usual Care)	Phase 2 (Walk 'n Watch)
Sequence A	**Number of patients screened**	160	118	102	97	89	160	406
(3 clusters)	Eligible	31	25	16	9	12	31	62
	Declined	10	10	2	4	4	10	20
	Missed Screening	0	0	1	0	0	0	1
	Consented	21	15	14	5	8	21	42
	Ineligible after Consent	3	1	0	0	0	3	1
	Withdrew before baseline	1	0	0	0	0	1	0
	Number of patients enrolled (completed baseline)	17	15	14	5	7	17	41
	Determined to be ineligible post-enrollment	1	0	0	2	0	1	1
	Included in primary analysis	16	15	14	4	7	16	40
	Completed trial protocol	16	14	12	4	6	16	36
	Completed follow-up	16	13	12	4	6	16	35
	Lost to follow-up	0	2	2	0	1	0	5
	Health reason	0	0	1	0	0	0	1
	Could not contact	0	0	0	0	1	0	1
	No longer interested	0	2	1	0	0	0	3
Sequence B	**Number of patients screened**	137	171	103	57	80	308	240
(3 clusters)	Eligible	30	19	18	11	8	49	37
	Declined	7	6	3	5	2	13	10
	Missed Screening	0	1	6	0	3	1	9
	Consented	20	13	15	6	6	33	27
	Ineligible after Consent	0	1	0	0	0	1	0
	Withdrew before baseline	0	0	0	0	0	0	0

	Number of patients enrolled (completed baseline)	20	12	15	6	6	32	27
	Determined to be ineligible post-enrollment	0	0	0	0	0	0	0
	Included in primary analysis	20	12	15	6	6	32	27
	Completed trial protocol	19	12	14	6	5	31	25
	Completed follow-up	19	11	14	5	5	30	24
	Lost to follow-up	1	1	1	1	1	2	3
	Health reason	0	0	1	1	0	0	2
	Could not contact	0	0	0	0	0	0	0
	No longer interested	1	1	0	0	1	2	1
Sequence C	**Number of patients screened**	171	124	122	138	133	417	271
(3 clusters)	Eligible	46	28	17	28	22	91	50
	Declined	19	8	4	7	7	31	14
	Missed screening	4	0	1	16	0	39	16
	Consented	23	19	12	21	15	56	36
	Ineligible after consent	1	2	1	3	0	4	3
	Withdrew before baseline	0	0	0	0	0	0	0
	Number of patients enrolled (completed baseline)	22	14	12	18	15	48	33
	Determined to be ineligible post-enrollment	2	0	0	0	1	2	1
	Included in primary analysis	20	14	12	18	14	46	32
	Completed trial protocol	20	12	12	18	14	44	32
	Completed follow-up	18	12	11	18	14	41	32
	Lost to follow-up	2	2	1	0	0	5	0
	Health reason	1	1	0	0	0	2	0
	Could not contact	1	1	0	0	0	2	0
	No longer interested	0	0	1	0	0	1	0
Sequence D	**Number of patients screened**	213	108	133	103	487	557	487
(3 clusters)	Eligible	50	23	24	16	78	113	78

Declined	16	5	10	9	30	40	30
Missed screening	3	0	0	0	19	3	19
Consented	33	18	12	7	48	70	48
Ineligible after Consent	0	0	0	0	1	0	1
Withdrew before baseline	0	0	0	0	1	0	1
Number of patients enrolled (completed baseline)	33	18	12	7	46	70	46
Determined to be ineligible post-enrollment	2	0	0	0	1	2	1
Included in primary analysis	31	18	12	7	45	68	45
Completed trial protocol	30	18	12	7	44	67	44
Completed follow-up	28	17	11	6	44	62	44
Lost to follow-up	3	1	1	1	1	6	1
Health reason	1	0	0	0	1	1	1
Could not contact	2	0	0	1	0	3	0
No longer interested	0	1	1	0	0	2	0
					Total Screened	**1442**	**1404**
					Total Enrolled	**167**	**147**
					Total Included in Primary Analysis	**162**	**144**
					Total Completed 4-week Follow-up	**149 (92%)**	**133 (92%)**

Note: 8 participants were enrolled but deemed to be ineligible post-enrolment (e.g., new brain imaging confirmed a diagnosis that was not a stroke; error in calculating their time post-stroke was found and made them ineligible, etc).

Table 2. Baseline characteristics of participants by group

Variable	Summary statistics	Whole cohort (N=306)	Usual Care (N=162)	Walk 'n Watch (N=144)
Age (years)	Mean (sd)	68 (13)	68 (12)	67 (13)
	Median (IQR)	68 [60, 77]	69 [60,77]	67 [60,77]
Days from stroke to study consent	Mean (sd)	29 (17)	29 (16)	27 (18)
	Median (IQR)	25 [15,38]	26 [18,39]	22 [15,36]
Baseline 6MWT (metres)	Mean (sd)	152 (106)	141 (101)	164 (110)
	Median (IQR)	130 [66, 225]	124 [57, 209]	140 [75, 237]
EQ5D index score	Mean (sd)	0·62 (0·19)	0·62 (0·20)	0·62 (0·18)
	Missing (%)	2 (0·7)	1 (0·6)	1 (0·7)
EQ5D VAS	Mean (sd)	56·8 (21·3)	57·8 (21·5)	55·6 (21·1)
	Missing (%)	3 (1·0)	2 (1·2)	1 (0·7)
MoCA total score	Mean (sd)	21·4 (6·1)	21·5 (5·9)	21·3 (6·3)
	Missing (%)	14 (4·6)	9 (5·6)	5 (3·5)
SPPB total score	Mean (sd)	4·0 (3·2)	3·9 (3·2)	4·1 (3·3)
	Missing (%)	3 (1·0)	2 (1·2)	1 (0·7)
SPPB 4-meter gait speed (m/s)	Mean (sd)	0·54 (0·30)	0·54 (0·31)	0·54 (0·29)
	Missing (%)	11 (3·6)	6 (3·7)	5 (3·5)
PHQ-9 total score	Mean (sd)	6·6 (5·1)	6·8 (4·9)	6·4 (5·3)
	Missing (%)	3 (1·0)	2 (1·2)	1 (0·7)
Resting blood pressure				
Systolic (mmHg)	Mean (sd)	124·9 (15·3)	124·7 (15·5)	125·2 (15·2)
	Missing (%)	1 (0·3)	0 (0·0)	1 (0·7)
Diastolic (mmHg)	Mean (sd)	74·8 (8·4)	74·7 (8·2)	75·0 (8·7)
	Missing (%)	1 (0·3)	0 (0·0)	1 (0·7)
Resting heart rate beats/min	Mean (sd)	78·4 (13·2)	77·8 (12·8)	79·1 (13·7)
	Missing (%)	2 (0·7)	1 (0·6)	1 (0·7)
Variable Frequency (%)				
Sex	Number (%)			
M		188 (61·4)	94 (58·0)	94 (65·3)
F		118 (38·6)	68 (42·0)	50 (34·7)
Race	Number (%)			
Black		2 (0·7)	1 (0·6)	1 (0·7)
East Asian		7 (2·2)	5 (3·1)	2 (1·4)
Indigenous		8 (2·6)	4 (2·5)	4 (2·8)
Latin American		1 (0·3)	0 (0·0)	1 (0·7)

South Asian		8 (2·6)	5 (3·1)	3 (2·1)
Southeast Asian		1 (0·3)	1 (0·6)	0 (0·0)
White		278 (90·8)	145 (89·5)	133 (92·3)
Mixed Race		1 (0·3)	1 (0·6)	0 (0·0)
Type of stroke	Number (%)			
Hemorrhagic		55 (18)	26 (16)	29 (20·1)
Ischemic		248 (81)	134 (82·7)	114 (79·2)
Unknown		3 (1·0)	2 (1·2)	1 (0·7)
Stroke location	Number (%)			
Cortical		94 (30·7)	42 (25·9)	52 (36·1)
Subcortical		149 (48·7)	84 (51·9)	65 (45·1)
Both		30 (9·8)	16 (9·9)	14 (9·7)
Missing		33 (10·8)	20 (12·3)	13 (9)
mRS score	Number (%)			
1		10 (3·3)	5 (3·1)	5 (3·5)
2		33 (10·8)	22 (13·6)	11 (7·6)
3		85 (27·8)	42 (25·9)	43 (29·9)
4		170 (55·6)	88 (54·3)	82 (56·9)
5		8 (2·6)	5 (3·1)	3 (2·1)
Site (Sequence, from Table 2)	Number (%)			
1 (A)		25 (8·2)	7 (4·3)	18 (12·5)
2 (A)		11 (3·6)	5 (3·1)	6 (4·2)
3 (A)		20 (6·5)	4 (2·5	16 (11·1)
4 (B)		18 (5·9)	6 (3·7)	12 (8·3)
5 (B)		30 (9·8)	20 (12·3)	10 (6·9)
6 (B)		11 (3·6)	6 (3·7)	5 (3·5)
7 (C)		25 (8·2)	14 (8·6)	11 (7·6)
8 (C)		38 (12·4)	23 (14·2)	15 (10·4)
9 (C)		15 (4·9)	9 (5·6)	6 (4·2)
10 (D)		41 (13·4)	27 (16·7)	14 (9·7)
11 (D)		27 (8·8)	19 (11·7)	8 (5·6)
12 (D)		45 (14·7)	22 (13·6)	23 (16)

Legend: 6MWT=6-Minute Walk Test, F=female, IQR=interquartile range, L=left, M=male, m/s=metres per second, MoCA=Montreal Cognitive Assessment, mRS=modified Rankin Scale, PHQ-9=Patient Health Questionnaire, R=right, SD=standard deviation, SPPB=Short Performance Physical Battery, VAS=Visual Analogue Scale

Table 3. Time-trend adjusted mean outcomes by treatment group. Values represent the estimated mean outcomes if all participants had been enrolled on the first day of trial enrollment. Raw 4-week means are not presented as they are not comparable due to confounding by time in the stepped-wedge trial design. Analysis set includes participants with non-missing values at both baseline and 4-weeks.

	Mean outcomes (SD); 4-week values adjusted for estimated time trend			
	Usual Care		Walk & Watch	
	Baseline	4-weeks	Baseline	4-weeks
6MWT, m	137.1 (100.9)	223.6 (130.4)	163.6 (112.7)	297.2 (133.2)
EQ5D index score	0.62 (0.20)	0.77 (0.17)	0.63 (0.18)	0.83 (0.16)
EQ5D VAS	57.5 (21.4)	70.8 (19.1)	56.2 (20.8)	77.9 (17.8)
MoCA	21.4 (6.0)	22.8 (5.6)	21.6 (6.0)	23.0 (5.2)
SPPB	3.7 (3.2)	6.8 (3.3)	4.0 (3.2)	8.2 (3.3)
Gait speed, m/sec	0.53 (0.31)	0.77 (0.39)	0.53 (0.29)	0.91 (0.39)
PHQ-9	6.9 (5.0)	4.0 (4.6)	6.3 (5.3)	2.6 (4.3)
Systolic BP, mmHg	124.7 (15.7)	127.2 (14.4)	125.9 (15.4)	127.0 (14.7)
Diastolic BP, mmHg	74.6 (8.2)	74.5 (8.4)	75.1 (8.7)	73.2 (9.2)
Heart rate, bpm	77.5 (12.9)	76.3 (13.6)	79.5 (13.9)	78.2 (13.6)
mRS <=2, %	12.8 (33.3)	46.1 (49.6)	10.4 (30.6)	59.7 (0.50)

Legend: 6MWT=6-Minute Walk Test, MoCA=Montreal Cognitive Assessment, mRS=modified Rankin Scale, PHQ-9=Patient Health Questionnaire, SPPB=Short Performance Physical Battery, VAS=Visual Analogue Scale

Table 4. Effectiveness of Walk 'n Watch compared to Usual Care

	Difference Between Walk 'n Watch versus Usual Care		
Outcome	**Mean**	**SE**	**95% CI**
Primary – 6MWT Improvement			
Intent-to-treat, metres	**43·6**	**16·5**	**[12·7, 76·1]**
Male subgroup, metres	64·1	17·9	[28·3, 99·9]
Female subgroup, metres	15·7	19·5	[-23·3, 54·7]
Per protocol, metres	52·6	19·1	[16·3, 89·4]
Secondary			
EQ5D index score	0·055	0·031	[-0·004, 0·116]
EQ5D VAS	8·0	3·5	[1·0, 14·6]
MoCA	0·02	0·60	[-1·14, 1·18]
SPPB	1·15	0·51	[0·18, 2·13]
Gait speed, metres/second	0·134	0·066	[0·010, 0·262]
PHQ-9	-1·09	0·72	[-2·50, 0·32]
Systolic BP, mmHg	-0·5	2·6	[-5·8, 4·4]
Diastolic BP, mmHg	-1·6	1·5	[-4·8, 1·2]
mRS ≤ 2	1·73*	--	[0·68, 4·44]*

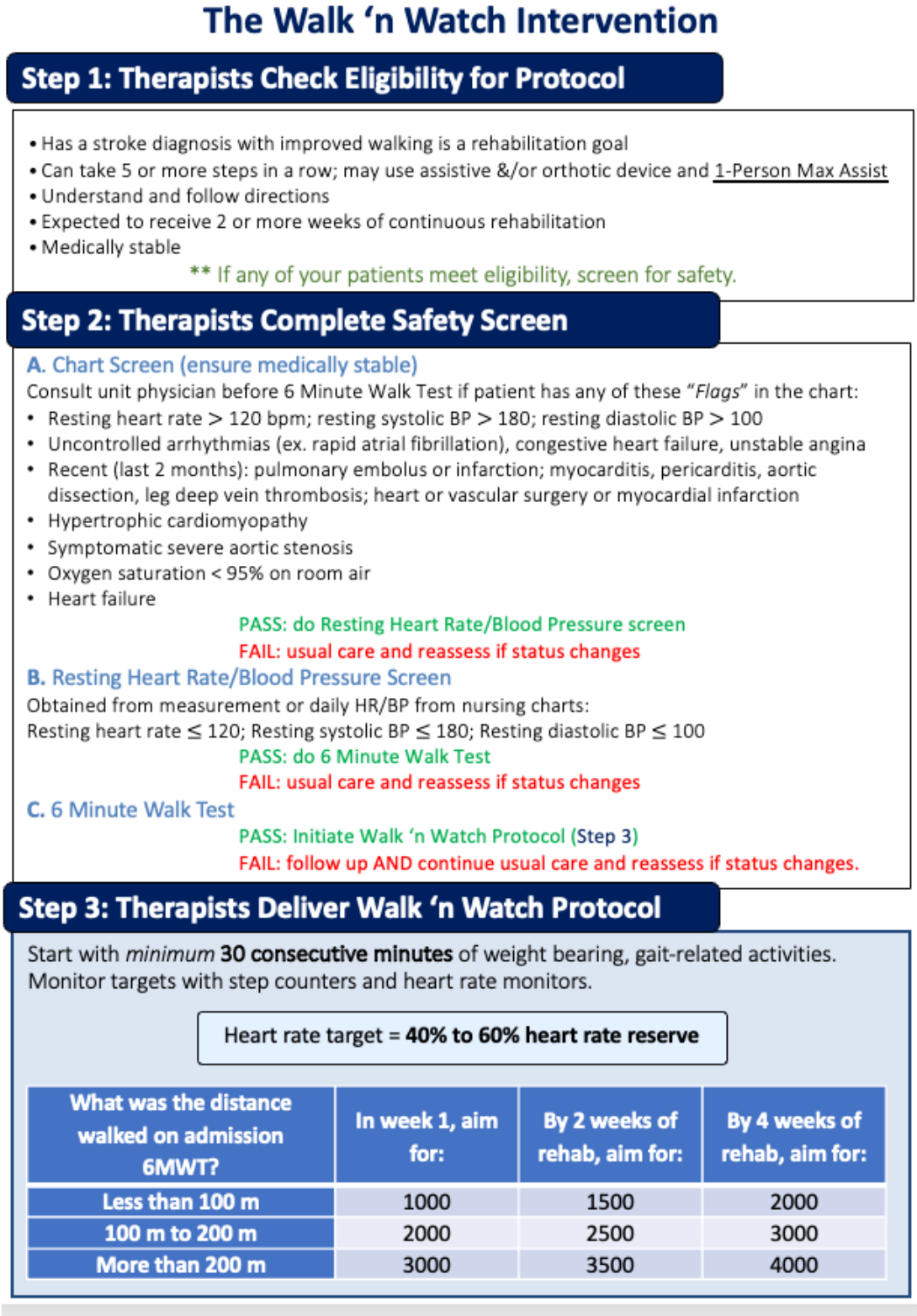
* Odds ratio. Odds of receiving a good outcome of mRS≤ 2 with 95%CI

Legend: 6MWT=6-Minute Walk Test; BP=Blood Pressure; CI=Confidence Interval; MoCA=Montreal Cognitive Assessment; mRS=modified Rankin Scale; PHQ-9=Patient Health Questionnaire; SE=Standard Error; SPPB=Short Performance Physical Battery; VAS=Visual Analogue Scale.

Table 5. Adverse Events

Study Group	Severe Adverse Event	Adverse Event
Usual Care	**n = 4**	**n = 31**
	Increased vertigo and diaphoresis (1) Bladder complication (1) Suspected seizure with fall in washroom (1) Suspected recurrent stroke on home visit (1)	Falls (n=29 by 22 patients) Hospital Room (5) Washroom (7) In therapy (0) Other location (17) Musculoskeletal Pain (1) Urinary retention (1)
WnW	**n = 5**	**n = 30**
	Arrhythmias while on the rehabilitation unit (1) Pseudoaneurysm (1) Severe COVID (1) Suspected recurrent stroke (had not started WnW) (1) Aspiration pneumonia (1)	Falls (n=29 by 24 patients) Hospital Room (8) Washroom (7) In therapy (1) Other location (13) Musculoskeletal Pain (n=1)

Figure 1. Walk 'n Watch Intervention



Data availability

De-identified participant data of the data utilized in this paper will be available at https://borealisdata.ca/dataverse/eng at 6 months following publication.

Contributors

SP and JJE contributed to Conceptualisation; JJE to Funding Acquisition; SP, JJE and SHH to the Original Draft; HW, YY, JJE and SP to Analysis (including directly accessing and verifying the underlying data); all authors contributed to Methodology, Review and Editing and had final responsibility for the decision to submit for publication (SP, SHH, MTB, KB, LAC, SD, SPD, VE, MHM, BMS, LS, HW, YY, JY, JJE).

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