Maximum tolerable daily dose of mirror movement therapy ankle exercises after stroke: an early phase dose screening study

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Abstract

Background Mirror movement therapy may reduce lower limb motor impairment after stroke. The dose is unknown.

Objective identify the maximum tolerable dose a day (MTD) of lower limb mirror movement therapy

Design 3 + 3 cohort rule-based, dose escalation/de-escalation study. After undertaking baseline measures participants performed mirror movement therapy for 14 consecutive days. Participants then undertook outcome measures. Cohort One trained for 15 minutes daily. Subsequent cohorts exercised at a dose set according to pre-set rules and the modified Fibonacci sequence. The study stopped when the difference between set doses for consecutive cohorts was 10% or less.

Setting Participants' homes (intervention) and a movement analysis laboratory (measures).

Participants Adults discharged from statutory stroke rehabilitation services.

Intervention Mirror movement therapy ankle exercises.

Outcome measures Motricity Index (primary) and bilateral time symmetry from movement onset to peak activation of Tibialis Anterior muscles during standardised sit-to-stand (secondary).

Results Five cohorts of three participants were included (n = 15). Mean (SD) age and time after stroke were 61 (9) years and 35 (42) months respectively. Set daily doses for the five cohorts were: 15, 30, 50, 40 then 35 minutes. The set dose for a subsequent cohort (six) would have been 38 minutes thus the difference from cohort five would have been three minutes i.e., 9% different. Therefore, the study stopped

Conclusion The identified MTD of lower limb mirror therapy was 35 minutes daily when frequency was set at seven days a week and duration as two weeks.

Clinical Trial Registration number NCT04339803 (ClinicalTrials.gov)

Contribution of the Paper This early phase study found that the maximum tolerable dose per day (MTD) of mirror movement therapy ankle exercises was 35 minutes when frequency was set at seven days a week and duration as two weeks. The optimal therapeutic dose will therefore be somewhere in the range of 15 (starting dose) to 35 minutes per day. Further dose articulation studies are required to identify the optimal therapeutic dose before use of findings in clinical practice. This study is the first step in that research process.

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Introduction

Mirror movement therapy (MMT) may be beneficial for recovery of lower limb motor function, walking speed, and mobility according to meta-analyses published in the Cochrane Library [1] and elsewhere since 2018 [2–4] (search strategy in online supplement). Notably, MMT has potential for home-based rehabilitation as it does not require digital technology expertise or space in homes for large items of equipment such as treadmills and exercise cycles. Indeed, MMT equipment, co-designed with stroke survivors and clinical therapists, can be set up/down using only one hand, and is storable in small spaces in peoples' homes [5]. For example, under a sofa. However, despite probable benefit the optimal dose of MMT for lower limb rehabilitation remains unknown [2–4]. Indeed systematic reviews published since 2018 [1–4] included published full paper articles of primary studies which reported a wide range of dosing parameters [6,7,16–25,8–15] (Table 1). These doses do not appear to have been based on the findings of precursor dose-finding studies. A PubMed Central search from 2017 to January 2022 using words "stroke" (title) and "mirror" (title) found three additional studies of MMT for the lower limb [26–28]. In these published reports no precursor dose-finding studies were referenced. They also used a range of dose parameters (Table 1).

This gap in the clinical trial pipeline for MMT evaluation is unsurprising as dose-finding is rarely conducted for stroke rehabilitation therapies [29]. Importantly, rehabilitation dose is multidimensional requiring consideration of: the daily amount (session length), the number of days a week (frequency), and the number of weeks for which therapy continues (duration) [30]. First, early-phase dose articulation trials are required to identify the maximum tolerated dose [31]. This could be effected with a study design adapted from pharmaceutical methods for dose screening of physical therapy interventions [32].

The aim of this study was to identify the maximum tolerable dose per day (MTD) of mirror therapy for the lower limb with frequency (number of sessions each week) and duration (length of the intervention in weeks) fixed.

Table 1

Parameters of dose of mirror movement therapy for the lower limb used in primary studies included in four systematic reviews and [1–4] subsequent studies.

Primary study	Dose parameters		
	Session length (minutes per day)	Frequency (days per week)	Duration (number of weeks)
Included in systematic reviews [1–4]			
Arya et al. 2017 [6]	30	3–4	12
Bahrami et al. 2013 [7]	30	3–5	Up to 4
Cha and Kim 2015a [8]	20	5	4
Cha and Kim 2015b [9]	30	5	4
De et al. 2017 [10]	60	5	4
Haiyan et al. 2017 [11]	30	3	8
Haiyan et al. 2017 [12]	15	6	4
In et al. 2016 [13]	30	5	4
Ji et al. 2014 [14]	20	5	6
Ji and Kim. 2015 [15]	15	5	4
Kawakami et al. 2015 [16]	20	5	4
Kim et al. 2016 [17]	30	5	4
Lee et al. 2016 [18]	60	5	4
Lee et al. 2017 [19]	30	3	6
Marquez et al. 2012 [20]	15	5	3
Mohan et al. 2013 [21]	30	6	2
Salem and Huang. 2015 [22]	30	5	4
Sutbeyaz S et al. 2007 [23]	30	5	4
Wang et al. 2017 [24]	40	5	6
Xu et al. 2017 [25]	30	5	4
Additional studies[a]			
Kim et al. 2018 [26]	no information[b]	5	4
May et al. 2020 [27]	30	5	4
Kim et al. 2021 [28]	60	5	8

a = PubMed Central search from 2017 to January 2022: "stroke" (title) and "mirror" (title).

b = no time provided. Participants performed 5 sets of 30 repetitions of the task a day.

Methods

Design, ethics, and trial registration

A 3 + 3 rule-based, dose escalation/de-escalation (dose screening) study was conducted [32]. The study started with the first cohort (n = 3), then each of the subsequent cohorts were also of three participants.

Ethical approval for this study was granted through the UK Health Research Authority (Identifier, 19/LO/0422). All participants provided written informed consent.

After providing ethical approval the UK Health Research Authority (HRA) placed a summary of the protocol on their website https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/dose-finding-of-lower-limb-mirror-therapy-after-stroke/. The HRA classified the study as experimental and therefore not requiring registration on a clinical trials database. Subsequently, the HRA asked the research team to register one of their other ongoing ethically approved early phase studies on a clinical trials database. No such request was received for the study reported here. Nevertheless, the research team then registered this study on ClinicalTrials.gov with ID: NCT04339803.

Participants, recruitment, and sample size

All participants were:

- aged at least 18 years, six weeks or more after stroke and discharged from NHS statutory stroke rehabilitation;
- able to produce some voluntary contraction of the more impaired ankle joint as measured by a Motricity Index score of 9–19 [33];
- able to follow a one-stage command;
- able to walk independently indoors before the index stroke and had not had a lower limb injury in the previous six months;
- had at least 50% passive range of motion in the more impaired ankle;
- were considered free of any condition that could be exaggerated by performing mirror therapy.

Participants were recruited from: an early supported discharge service, stroke support groups, and people who contacted the Researcher after hearing about the study from a friend.

Sample size was not set before the study began. For dose-screening studies the sample size is determined by the response of cohorts to the set dose and application of the pre-set rules [34,35].

Procedure: participant pathway

After providing informed consent, participants were given an appointment to visit the Movement and Exercise Laboratory at the University of East Anglia (MoveExLab).

At this first (baseline) visit they undertook primary and secondary measures. Then they were trained how to set-up, use and set-down the mirror therapy equipment before being informed of their set daily dose of mirror therapy ankle exercise. Before leaving the MoveExLab, participants undertook their first daily dose supervised by a Researcher. On the subsequent 13 days they were asked to undertake their daily dose at home unsupervised. Participants were provided with a stopwatch and a form so that they could record the number of minutes they achieved on each intervention day. If, because of fatigue, they needed to split the daily dose across sessions they were asked to record the number of minutes for each session. For any day on which they were unable to complete the dose they were asked to record the reason e.g., fatigue, hospital appointment. During the intervention period a Researcher contacted participants via telephone at least twice to resolve any challenges that could arise.

Participants returned to the MoveExLab on their 14th intervention day, or up to two calendar days later, to repeat the measures (outcome). One of the 15 participants (participant 11 in cohort four) was unwell and therefore undertook outcome measures eight days after the end of the intervention phase. At the outcome visit participants returned the mirror therapy equipment.

Procedure: starting dose and subsequent doses

The starting daily dose (first cohort) was 15 minutes as this is the shortest session length used in studies included in systematic reviews (Table 1). Then, the second and subsequent cohorts exercised at a dose set in accordance with the nine pre-set rules and the modified Fibonacci sequence (mFBS: Table 2). All daily doses were to be undertaken on 14 consecutive days as two weeks is the shortest duration reported (Table 1).

Procedure: pre-set rules

Decisions about whether to escalate/de-escalate the dose for subsequent cohorts and to stop the study were made in accordance with nine published pre-set rules and the modified Fibonacci sequence (Table 2) [32]. The nine pre-set rules were informed by those used in the earlier study [32]. The dose to which the stopping rules applied was designated as the maximal tolerated dose (MTD). Dose tolerability and dose benefit were central to application of the pre-set rules.

A tolerable dose was defined as when at least two of three participants adhered to the set dose for that cohort. If participants were unable to adhere for a reason related to their daily life, such as a hospital appointment, they were still considered adherent. Otherwise, if the set dose was not completed it was deemed not tolerable.

A beneficial dose was defined as when at least two of three participants demonstrated an improvement in outcome

Table 2
The nine pre-set study rules and Modified Fibonacci sequence (mFBS).

The nine pre-set study rules	
1	The target dose was not achieved by all three participants then the consequent action was to decrease the dose by 50% of the previous increment for the subsequent cohort.
2	The target dose was tolerable and beneficial for a cohort. The consequent action was to increase the dose for the subsequent cohort.
3	If the target dose was not tolerable for the cohort, then rule 6 was applied.
4	If the target dose was tolerable but not beneficial:
i	If there was no change in the dose benefit measure pre and post the training points for at least two of the three participants, then rule 7 was followed.
ii	If there was a decrease in the dose benefit measure between the pre- and post- training measure for at least two of the three participants, the dose of the subsequent cohort was decreased by 50% of the previous changes.
5	If the dose was decreased for a cohort and then deemed tolerable and beneficial, the action for the subsequent cohort was to increase the dose by 67% of the previous change.
6[a]	If the dose was not tolerable for two of the three participants, the next cohort received the same target dose. If this dose was not tolerable for the two participants in the second cohort, the next cohort was decreased by 50% of the last increment
7[a]	If a particular dose was tolerable but not beneficial for at least for two participants of the three, then mFBS informed increase of the dose for of the subsequent cohort. If that second cohort also did not show at least one level of improvement in the outcome measure, then stopping rules were considered.
8[b]	If after at least one beneficial dose, the subsequent two target doses were tolerable, but no further gains in motor function outcome were made in at least two participants in each of two consecutive cohorts, the study was stopped.
9[b]	If the dose difference between the two cohorts was equal to or less than 10%, the study was stopped
Dose (D) increments for subsequent cohorts informed by the mFBS	
Cohort 1	D_1
Cohort 2	$2.00 \times D_1$
Cohort 3	$1.67 \times D_2$
Cohort 4	$1.50 \times D_3$
Cohort 5	$1.40 \times D_4$
Cohort 6	$1.33 \times D_5$
Cohort 7	$1.33 \times D_6$
Cohort 8+	$1.33 \times D_{7+}$

[a] Checking rules;
[b] Stopping rules

measurement over the two-week training period. For each participant the process was to first consider the primary outcome measure. If this did not increase, then the secondary measure was considered.

Mirror therapy intervention

The MMT equipment used in this study was co-designed with stroke survivors and clinical physiotherapists for undertaking ankle exercise (MMT-ankle) to improve ability to produce voluntary movement of the more affected ankle joint (Fig. 1) [5]. Ankle exercise was the focus as it is a component of therapy for improving walking endurance and sit-to-stand ability [36].

Participants sat in a chair that allowed them to maintain an upright posture with their hips, knees, and ankles at 90 degrees when feet were flat on the ground. They placed the MMT-ankle equipment in their front midline. Participants were asked to place their bare feet on the instep supports and use the fabric provided to cover the more affected lower limb. From this starting position they were asked to repeatedly move their less affected foot up and down, pivoting on the instep support, to perform ankle dorsi-flexion and plantar-flexion. If possible, they performed the movement bilaterally as this may be more effective than unilateral exercise for MMT-ankle [2,3]. During the exercise

they were asked to watch the reflection of their less affected lower limb in the mirror whilst maintaining an upright posture (Fig. 1). They were asked to concentrate on the mirror reflection and avoid any external distraction such as watching the television. Splitting the daily dose across training sessions during a day was allowed to minimise fatigue.

Primary outcome measure

The focus of the intervention was the ability to produce voluntary movement of the more affected ankle and was measured with the Motricity Index lower ankle section [33]. Scores range from 0 to 33. For this study an increase of at least one level between baseline and outcome was considered an improvement.

Secondary outcome measure

The secondary outcome measure was focused on the ability to produce muscle activity in the more affected Tibialis Anterior muscle during a standardised sit-to-stand task. This neuromuscular measure was undertaken in consideration of the possibility that the Motricity Index might not have been sufficiently sensitive to detect benefit from MMT-ankle over a 14-day period. The

Fig. 1. Mirror Movement Therapy ankle exercise modelled by a researcher.

specific measure was symmetry of the time from onset of movement to peak activation in the more and less affected Tibialis Anterior muscles derived from surface electromyography (sEMG). For this study, a change of at least 10% towards symmetry was considered an improvement.

Participants changed into shorts and removed any lower limb orthosis. Then they sat on a plinth the height of which was adjusted to allow hips, knees, and ankles at 90 degrees and feet flat on the floor. For each participant the plinth height from the floor, and distance from the knee to plinth were recorded at baseline and replicated at the outcome measurement session. Participants were asked to sit still until they heard the 'go' signal, a buzzer, and then stand up independently without using their arms to push up. Any trials in which arms were used or physical assistance was provided were discarded.

Muscle activity data was collected at 2000 Hz from sEMG sensors (Delsys Trigno, Massachusetts, USA) placed over the Tibialis Anterior muscles in accordance with the SENIAM Guidelines http://www.seniam.org. Kinetic data was collected at 1000 Hz from two separate Bertec forceplates (Bertec, Ohio, USA) one under each foot. All data were synchronised through the Vicon Nexus software (Vicon, Oxford, UK).

Raw synchronised, 'go' signal-marked, kinetic and sEMG data were then exported from Vicon Nexus software to a CSV file for each trial. A purpose made Spyder (Python 3.7) script was run on each sEMG CSV file for data extraction. For sEMG data the DC offset was removed and a band pass high level 20 Hz, low level 450 Hz was applied. Data were then rectified, and a Butterworth filter 4th order filter, frequency 10 Hz, was applied to create an EMG envelope. Then, resting means were calculated for force plate and EMG data using 10 s of data before the 'go' signal. Movement onset occurred when the vertical force (Fz) on either force plate reached or exceeded the resting mean ± 2 standard deviations. Then the time between onset of movement and peak sEMG activity was calculated for both TA muscles for each trial. From these values, mean times were calculated for each participant for both muscles.

Symmetry of the time from onset of movement to peak activation in the more and less affected Tibialis Anterior muscles was calculated for each participant using the equation: (2 x more affected muscle) / (more affected muscle + less affected muscle) – 1 [37]. Therefore, positive values would indicate a bias towards the more affected muscle.

In the protocol registered in ClinicalTrials.gov (Identifier: NCT04339803) it was planned to also investigate neurophysiological substrates of Tibialis Anterior muscle activity. Planned measures were spinal excitability as measured by the Hoffmann reflex (H-reflex), and corticospinal excitability derived from transcranial magnetic stimulation (TMS). However, six participants in early cohorts had contraindications to TMS. Then, later in the study, procedures to minimise risk of transmission of the COVID virus required reduction of the time researchers spent close to participants. Therefore, collection of these additional secondary measures ceased.

Dose decision-making

Outcomes for each cohort were used by two Researchers, working independently before triangulating, to inform the dose decision for the next cohort. This was undertaken in accordance with the pre-set rules and the mFBS (Table 2). The Motricity Index scores, primary outcome, were considered first. If the set dose was found to be beneficial for a cohort, then the secondary outcome measure was not considered. If the Motricity Index did not improve for a cohort then the researchers considered the secondary outcome, symmetry of the time from onset of movement to peak activation in the Tibialis Anterior muscles.

Results

Participants

Details of participant recruitment and flow through the study are provided in Fig. 2. Essentially, 16 participants
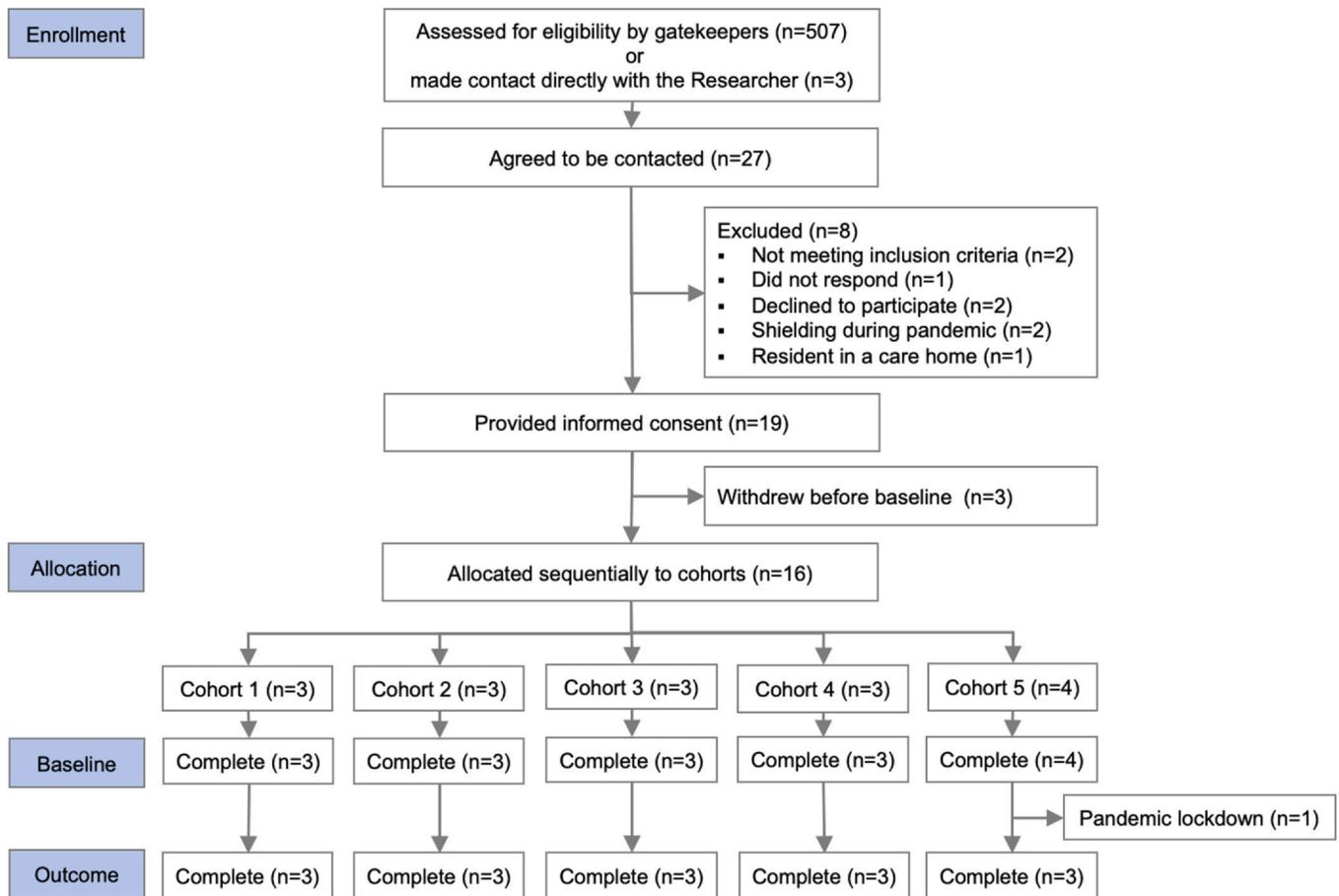
Fig. 2. Participant recruitment and flow through the study.

completed baseline measures and were allocated sequentially to one of the five cohorts. One participant was withdrawn because of lockdown during the pandemic and therefore 15 completed outcome measures.

Characteristics of the 15 participants are provided in Table 3. In summary, the mean (SD) age of the 10 males and 5 females was 60.5 (9.4) years. Their mean (SD) time after stroke was 34.5 (42.4) months.

Identification of the Maximal Tolerable Dose (MTD) per day

The pre-set rules together with the mFBS (Table 2) and definitions of dose tolerability and dose benefit (in methods) were used to identify the MTD. Data for each cohort are given in Table 3. A summary for each cohort is given Table 4.

All participants in cohort one adhered to the set dose of 15 minutes and two showed benefit in the primary outcome. Therefore, the dose doubled for cohort two.

All cohort two participants adhered to the set dose of 30 minutes but only one showed improvement in the primary outcome. So, the secondary outcome was con-

sidered. An improvement was found for only one participant. Therefore, rules 4i and 7 were applied. Consequently, the dose for cohort three was increased to 50 minutes.

None of the participants in cohort three adhered to the set dose of 50 minutes. Therefore, rule 1 was applied to decrease the dose by 50% of the previous increment and the subsequent cohort was set a dose of 40 minutes.

In cohort four, two participants adhered to the set dose of 40 minutes but showed no improvement in the primary outcome. So, the secondary outcome was considered. This showed a decrease of more than 10% from baseline for two participants and rule 4ii was applied to decrease the dose by 50% of the previous change. The subsequent cohort was assigned a dose of 35 minutes.

All participants in cohort five adhered to the set dose of 35 minutes but only one showed an improvement in the primary outcome. The secondary outcome showed an improvement for two participants. Rule 5 was applicable and indicated an increase of 67% of the previous change. However, an increase of three minutes was less than 10% different from cohort five. Rule 9 applied to stop the study on a set dose of 35 minutes.

Table 3
Participants' characteristics at baseline.

	Cohort 1 (n = 3)	Cohort 2 (n = 3)	Cohort 3 (n = 3)	Cohort 4 (n = 3)	Cohort 5 (n = 3)	All cohorts (n = 15)
Mean age, years (SD, range)	52.3 (9.9, 41.0–59.0)	59.3 (2.3, 58.0–62.0)	64.0 (11.3, 51.0–71.0)	67.7 (11.7, 55.0–78.0)	59.0 (21.6, 51.0–66.0)	60.5 (9.4, 41.0–78.0)
Mean time after stroke, months (SD, range)	39.6 (29.3, 6.0–59.0)	71.3 (84.7, 10–168)	28.7 (25.1, 5.0–55.0)	27 (21, 6–48)	5.7 (4.9, 3.0–10.0)	34.5 (42.4, 3.0–168)
Number (%) female	0 (0%)	2 (67%)	3 (100%)	0 (0%)	0 (0%)	5 (33%)
Number (%) with right side more impaired	2 (67%)	2 (67%)	1 (33%)	1 (33%)	2 (67%)	8 (53%)
Mean Motricity Index[a] (SD, range)	12.3 (2.88, 9–14)	9.0 (0.0, 9.0–9.0)	15.7 (5.77, 9–19)	10.7 (2.88, 9.0–14.0)	12.3 (5.8, 9.0–19.0)	12.0 (4.1, 9.0–19.0)

SD = standard deviation

[a] = more paretic ankle

Discussion

This study found that the maximum tolerable dose (MTD per day of MMT-ankle was 35 minutes when frequency was set at seven days a week and duration at two weeks. After five cohorts of three participants were included, the study was stopped because the dose difference between two consecutive cohorts would have been less than 10%. This is probably the first dose-screening study of MMT-ankle and the findings address the need for information for subsequent studies investigating the optimal dose [2–4].

Controlled studies included in systematic reviews and those published subsequently reported daily dose of lower limb MMT as 15, 20, 30, 40 or 60 minutes [1–4,27,28] or as number of repetitions [26] (Table 1). The majority, 52%, reported a planned provision of 30 minutes a day. However, a robust dose screening study was needed to begin the process of identification of the optimal dose. The MTD of 35 minutes identified in this study for MMT-ankle has resulted from sufficient use of a systematic approach to early phase rehabilitation trials [38] recognising the importance of building the knowledge units required to conduct robust efficient clinical trials to avoid research waste [39]. Moreover, it is unclear whether the planned daily doses in earlier studies were delivered as participants' adherence to set dose was not reported. Not reporting adherence makes interpretation of findings difficult [40,41]. Other impediments to direct comparison are the setting for the intervention, whether supervision is provided and combining mirror therapy with other intervention e.g., neuromuscular stimulation. The study reported here, provides the MTD per day of MMT-ankle alone (not combined with another therapy) conducted at home by stroke survivors who received no in-person supervision of practice in alignment with how most therapy is delivered in practice.

Table 4
Data that informed dose decisions for sequential cohorts and triggered a stopping rule.

Cohort	Participant	Target dose (minutes)	Minutes performed (mean)	Dose tolerable	Motricity Index more impaired ankle (MI)			TA symmetry value			Dose beneficial
					MI at baseline	MI at outcome	Changed one level or more	Baseline	Outcome	Improved 10% or more	
1	1	15	15	Yes	14	14	No	NA			Yes
	2		15		9	14	Yes				
	3		15		14	25	Yes				
2	4	30	30	Yes	9	9	No	0	0.040	No	No
	5		30		9	9	No	-0.135	-0.090	Yes	
	6		30		9	14	Yes	0	-0.107	No	
3	7	50	46	No	19	19	No	NA			NA
	8		43		9	9	No				
	9		36		19	25	Yes				
4	10	40	38*	Yes	9	9	No	0.044	0.162	No	No
	11		26		9	14	Yes	-0.046	-0.127	No	
	12		40		14	14	No	0.174	0.185	No	
5	13	35	35	Yes	9	9	No	0.287	0.133	Yes	Yes
	14		35		9	9	No	-0.070	-0.050	Yes	
	15		35		19	25	Yes	EE	EE	EE	

NA = not applicable as beneficial dose identified by Motricity Index change or dose was not tolerable   EE = equipment error during data collection therefore values could not be calculated

* = participant had a hospital appointment therefore considered adherent

A potential limitation of this study is the heterogeneity between participants for age and time after stroke. Compared to the mean age of stroke survivors in the UK, 75 years [42], participants in this study were younger with a mean age of 61 years (Table 3). It is possible that older people will have a lower MTD than 35 minutes. However, cohort four, mean age 68 years, tolerated a set dose of 40 minutes. Participants' time after stroke ranged between three and 168 months (Table 3) which could have influenced potential for improvement in motor impairment. However, late after stroke substantial reduction in motor impairment in response to rehabilitation has been reported [43,44]. Nevertheless, the potential influence on the MTD of age and time after stroke deserve further investigation in the required subsequent dose-articulation studies. These studies could include investigation of the reasons that stroke survivors may not tolerate more than 35 minutes a day of MMT.

A key strength of this study is the systematic application in real-life home-based rehabilitation of the rule-based, dose escalation/de-escalation (dose screening) design previously developed in a methodological study [32]. Importantly, this study demonstrates that dose screening studies can be undertaken in participants' homes. This is important because there is an increasing emphasis on home-based rehabilitation after stroke and on self- rehabilitation [45]. However, it is possible that participant's self-report might not agree with an objective assessment of minutes a day of performing mirror therapy. So, subsequent dose articulation studies to identify the optimal therapeutic dose need an objective measure of time spent performing mirror therapy.

The most obvious strength of this study is that this is, to the best of the authors' knowledge, probably the first-ever identification of a MTD for MMT and specifically for MMT-ankle. Also, an important strength is that this study has demonstrated the dose-screening design developed with a model rehabilitation intervention is applicable to real-life physical therapy.

The findings of this study have relevance for contemporary clinical practice in which rehabilitation settings are often peoples' homes and use of self-rehabilitation to complement therapist-present therapy [45]. However, this study is just the first step towards identification of the optimal therapeutic dose (OTD) for testing in clinical efficacy trials the results of which will inform clinical practice. Therefore, use of these preliminary findings in clinical practice is not advisable at present. Although the MTD identified is 35 minutes a day, the optimal therapeutic dose (OTD) will therefore be somewhere between 15 (starting dose) and 35 minutes per day. Also, it is possible that a longer duration and/or a different frequency of MMT-ankle is needed for optimal benefit. Further dose articulation studies are required to find the OTD of MMT-ankle to be tested in clinical efficacy trials. This study is the first step in that process [31].

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Conflict of interest statement

Valerie M. Pomeroy is an Associate Editor and was not involved in the peer review of this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.physio.2023.10.007.

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