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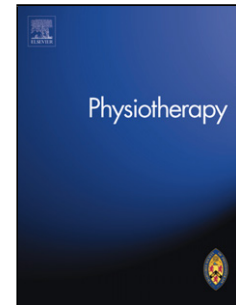
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# **A rule-based, dose-finding design for use in stroke rehabilitation research: methodological development**

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**Abstract**

**Background** Dose-optimisation studies as precursors to clinical trials are rare in stroke rehabilitation.

**Objective** To develop a rule-based, dose-finding design for stroke rehabilitation research.

**Design** 3+3 rule-based, dose-finding study. Dose escalation/de-escalation was undertaken according to pre-set rules and a mathematical sequence (modified Fibonacci sequence). The target starting daily dose was 50 repetitions for the first cohort. Adherence was recorded by an electronic counter. At the end of the 2-week training period, the adherence record indicated dose tolerability (adherence to target dose) and the outcome measure indicated dose benefit (10% increase in motor function). The pre-set increment/decrease and checking rules were then applied to set the dose for the subsequent cohort. The process was repeated until pre-set stopping rules were met.

**Participants** Participants had a mean age of 68 (range 48–81) years, and were a mean of 70 (range 9–289) months post stroke with moderate upper limb paresis.

**Model task** A custom-built model of exercise-based training to enhance ability to open the paretic hand.

**Outcome measure** Repetitions per minute of extension/flexion of paretic digits against resistance.

**Analysis** Usability of the pre-set rules and whether the maximally tolerated dose was identifiable.

**Results** Five cohorts of three participants were involved. Discernibly different doses were set for each subsequent cohort (i.e. 50, 100, 167, 251 and 209 repetitions/day). The maximally tolerated dose for the model training task was 209 repetitions/day.

**Conclusions** This dose-finding design is a feasible method for use in stroke rehabilitation research.

*Keywords:* Stroke rehabilitation; Dose finding; Physical therapy; Upper limb



**<A>Introduction**

Recommendations for higher doses of physiotherapy in stroke rehabilitation, based on findings from meta-analyses [1], are questioned by findings that higher doses may not always produce better recovery [2–5]. This could be because clinical recommendations based on meta-analyses of dose [6] may be insufficiently nuanced in respect of potential influential factors on dose response. Consideration of potential influential factors (e.g. type of intervention, time after stroke, severity of paresis) is difficult within meta-analysis because reports of primary trials do not always provide sufficient information [7]. Indeed, removal of the potential confounder of type of therapy diminishes the relationship between higher dose and better outcome [8]. These clinical findings are echoed in experimental studies of motor recovery in animal models and motor learning in healthy adult humans. Higher doses of therapy/training do not always provide better results [9–11].

In other areas of health care, the optimal therapeutic dose of specific interventions is frequently determined before undertaking clinical efficacy trials. Such dose-optimisation studies are needed for specific stroke rehabilitation interventions [12–14]. There are several parameters of dose to consider [15], including the maximum tolerable dose (MTD) and recommended Phase II dose (RPTD). These are listed and defined in Appendix 1 [16].

Pharmaceutical research employs two main dose-optimisation designs: dose-ranging and dose-finding [17]. Dose-ranging studies identify the response to, and safety of, a number of pre-specified doses identified through early-phase research. Dose-finding studies are classified as adaptive designs as they allow exploration of the dose–response relationship whilst minimising sample size and maintaining safety of participants [18–20].

The aim of this investigation was to develop a dose-finding design for stroke rehabilitation research, rather than to identify the MTD or RPTD of exercise-based physiotherapy. The specific objectives were:

- (1) to determine if all the features of the (pharmaceutical) dose-finding design are viable; and
- (2) to determine if the dose-finding design can identify the MTD and RPTD of a model of exercise-based therapy.

A model training task was used to minimise the possibility that the results of the methodological development investigation reported here could be used to inform the prescribed dose of exercise-based physiotherapy. If the design is feasible, it can be used in subsequent dose-ranging studies to check the RPTD for evaluation in later clinical efficacy trials.

## **<A>Methods**

### *<B>Design*

A single-arm, 3+3 rule-based, dose-escalation design (Fig. 1) was adapted for a motor rehabilitation intervention. The advantage of this design is that it provides an acceptable level of precision in finding the MTD, finds the RPTD, minimises sample size, and makes no prior assumptions about the dose–response relationship [16,18,20–22].

**<insert Fig 1 near here>**

The study began with the first cohort ( $n=3$ ) exercising at the target starting dose, 50 repetitions, for 5 days/week for a 2-week period (10 training days; Fig. 1). The second and subsequent cohorts exercised at a target dose set in accordance with the nine pre-set rules (see below) and the modified Fibonacci sequence (mFBS) (Table 1). The mFBS allows for rapid increase from the initial low dose for which minimal adverse consequences are likely. As dose increases, the occurrence of adverse consequences is likely to be greater, but the incremental increase is smaller. The mFBS also reduces the chance of implementation of subtherapeutic doses [23], and provides an adequate spread of doses for estimation of the dose–response relationship [22].

<insert Table 1 near here>

#### <C>Pre-set rules

Two definitions were used. A tolerable dose was defined as one where two or more participants adhered to the set dose for that cohort and, at most, only one participant experienced an adverse consequence. If a participant was unable to adhere to the target dose due to reasons unrelated to the design (e.g. hospital appointment) for  $\leq 3$  days over the 2-week period, they were still considered adherent. A beneficial dose was defined as an increase in the score of the dose-benefit measure (details below) by  $\geq 10\%$  over the training period (for at least two participants in a cohort).

The dose-setting rules (Rules 1 to 5), possible scenarios and their consequent actions were applied for each cohort at the assessment at the end of the training period (Fig. 1):

1. The target dose was not achieved by all three participants. The consequent action was to decrease the dose by 50% of the previous increment for the subsequent cohort (Fig. 1).

2. The target dose was tolerable and beneficial for a cohort. The consequent action was to increase the dose for the subsequent cohort (Fig. 1).
3. The target dose was not tolerable for a cohort. If this occurred, Rule 6 was applied (see ‘Checking rules’ below and Fig. 1).
4. If the target dose was tolerable for a cohort but not beneficial:
  - (a) if there was no change in the dose-benefit measure between the pre-training and post-training points for at least two of three participants, the consequent action was to implement Rule 7 (see ‘Checking rules’ below and Fig. 1).
  - (b) If there was a decrease in the dose-benefit measure between the pre-training and post-training points for at least two of three participants, the dose for the subsequent cohort was decreased by 50% of the previous increment (Fig. 1).
5. If a 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% (Sequence Point 3 of the mFBS, Table 1) of the previous increment (Fig. 1).

The checking rules (Rules 6 and 7) were applied to reduce the possibility of a dose being deemed not tolerable or not beneficial because of individuals, rather than the target dose itself:

6. If the dose was not tolerable for two of three participants, the next cohort received the same target dose. If this dose was not tolerable for two participants in the second cohort, the next cohort was decreased by 50% of the last increment (Fig. 1).
7. If a particular dose was tolerable but not beneficial for at least two participants, the mFBS informed increase of the dose for the subsequent cohort. If that second cohort also did not experience at least a 10% improvement in the outcome measure, the stopping rules were considered.

The stopping rules (Rules 8 and 9) were as follows.



8. If after at least one beneficial dose, the subsequent two target doses were tolerable but no further gains in motor function were made in at least two participants in each of the two consecutive cohorts, the study was stopped (Fig. 1).
9. If the dose difference between two cohorts was  $\leq 10\%$ , the study was stopped (Fig. 1).

*<B>Participants and sample size*

Participants were recruited from stroke survivor support groups. Each participant provided informed consent and:

- was aged 18 years or more;
- had received a clinical diagnosis of stroke at least 6 months previously, and thus was in the so-called ‘chronic phase’ when spontaneous recovery was not expected to confound response to the model of exercise-based physiotherapy used as the training task in this investigation;
- had the ability to open and close the paretic hand six times in 1 minute but was unable to do this 25 times in 1 minute when an extra-extra-light resistance band (DIGI-EXTEND) was placed around fingers and thumb;
- was able to imitate actions with the less-paretic upper limb. The researcher sat alongside the potential participant and performed the model training task (details below) five times using the extra-extra-light resistance band. The participant then performed the model training task five times with the less-paretic upper limb. Accuracy of imitation was scored as follows: 2 points = correctly reproduced; 1 point = incorrect reproduction; and 0 points = task not reproduced [24]; and
- was discharged from statutory stroke rehabilitation.

Target sample size is not usually pre-defined for dose-finding studies [19]. The final sample size is determined by the response of subsequent cohorts to the target dose. In pharmaceutical dose-finding studies, the reported sample sizes are generally between 12 and 40 [25].

*<B>Model training task, starting dose, adherence and study procedure for participants*

The training task was devised as a model of exercise-based physiotherapy to avoid the potential confounders of: (a) different training tasks for each participant; and (b) familiarity/prior training with the training task (Box 1). It focused on training synergistic extension/abduction and flexion/adduction of the paretic fingers and thumb against a tailored resistance in left and right workspace. The equipment (Fig. 2) comprised a custom-made wooden stand with two vertical tripods and resistance-graded rubber bands (DIGI-EXTEND). An elastic band was placed on the top one-third of one of the tripods. Participants placed their paretic fingers and thumb inside the band and then moved it on to the other tripod: this was one repetition. Moving it back to the first tripod counted as a second repetition, and so on. Each day, they performed the target number of repetitions (dose), which was split across the day if necessary.

**<insert Box 1 and Fig 2 near here>**

Exercise-based training is comprised of several dose components (Appendix 1). All of these were controlled apart from the amount (in this case, repetitions per session), as this was the dose component of interest. The training duration was 2 working weeks (10 days), and frequency was every working day. Intensity (effort required to perform the task) was set individually for each participant to maximise equivalence.

On their first trial day, the training intensity was set for each participant for 2 weeks. Intensity was determined as the resistance band with which an individual was able to complete six repetitions in 1 minute. Setting intensity began with the extra-light band. If this was too difficult, they were given the extra-extra-light band. Alternatively, if the extra-light band was too easy, the light band was tried, then the medium and so on until the correct band was identified.

To set the starting dose, it was considered that this is usually based on precursor studies that establish the safe minimal effective dose for pharmaceutical dose-finding studies (Appendix 1). Such precursor studies are unavailable for stroke rehabilitation. As such, the starting dose for the present study considered that experimental studies of animal models of stroke indicate that a beneficial dose may be between 240 [26] and 400 [27–31] daily repetitions, and that approximately 300 daily repetitions may be tolerable for stroke survivors [32,33]. It was also considered that the dose-setting rules allowed for rapid increments of the target dose, but it was necessary to ensure that the design feasibility was tested. Consequently, the conservatively low starting dose of 50 repetitions was chosen.

Adherence to target dose, tolerability was assessed via an electronic counter (Fig. 2). The number of repetitions and time spent in self-practice was recorded and stored electronically in a memory card. At the beginning of a training day, the participant switched on the counter and then pressed a red button to initialise the recording card. After each repetition, they pressed a black button. The counts were displayed on the integral monitor. At the end of each session, participants recorded the number of repetitions on a paper form to safeguard against any challenges with the memory card.

The study procedure began on the participants' first training day (Day 1) when they attended the Movement Laboratory for baseline measurement. The intensity of the training task was then set for each individual (described above). The participants' first training session was supervised by the researcher to ensure that the training task and recording of repetitions was undertaken correctly. On Days 2 to 7, participants

self-trained in their homes for 5 days. Participants returned to the Movement Laboratory on Day 8 for a check of how they were performing the task, recording repetitions, and to discuss any concerns or questions. They then self-trained at home for 5 of the remaining 6 days. On the day after the last training day (Day 14), participants attended the Movement Laboratory for outcome measurement, if possible. Up to 7 days were allowed in the ethically approved protocol for this post-training visit to avoid attrition due to public holidays, illness etc.

#### *<B>Dose-benefit measure*

The Cando Digit-Extend device (DIGI-EXTEND) was used to measure the number of repetitions in 1 minute of extension/flexion of fingers and thumb against the lightest resistance band whilst participants sat at a table on a dining-type armless chair. This measure was chosen as it required the same finger extension movement of the trained task, but was different in that no transportation of the hand was required horizontally across the workspace.

#### *<B>Adverse consequences*

If participants experienced any adverse occurrences, such as discomfort, pain and fatigue, on any of the training days, they noted these on the dose-monitoring form. The researcher also specifically asked them about adverse occurrences during their visits to the Movement Laboratory.

#### *<B>Analysis*

Dose-finding design feasibility was assessed through: time required to recruit participants and complete the study; and usability of the pre-set rules.

MTD was identified in accordance with the definition provided in Appendix 1. RPTD was identified by: (a) plotting the dose adherence rate by cohort; and (b) estimating the dose–response relationship using two standard curves (linear and quadratic), and using the one that provided the best fit [34]. Best goodness of fit was defined as the curve with the highest  $R^2$  (coefficient of determination) value, and RPTD is the maximum y-axis value for the curve. A non-parametric curve was plotted as a graphical gauge.

## <A>Results

Table 2 provides details of participants’ characteristics at baseline. In summary, the mean age of the 15 participants was 68 (range 48 to 81) years and the mean time post stroke was 70 (range 9 to 289) months.

<insert Table 2 near here>

<B>*Feasibility of the design*

<C>*Time required*

The trial recruitment period started in March 2014 and data collection ended in February 2015.

<C>*Pre-set rules*

Application of the mFBS with the dose-setting rules determined different target doses for subsequent cohorts [i.e. differences >10% (Table 3)]. Five cohorts were included. A sixth cohort was not recruited as the set dose would have been 237 repetitions. However, only 14 repetitions separated doses of 251 (Cohort 4) and 237, which was <10% of the difference (Table 3). Consequently, the trial was stopped at that point (Rule 9). The pre-set checking rules were not required during this study.

<insert Table 3 near here>

Adherence to target dose was important for the application of the pre-set rules. One participant reported getting confused about the correct procedure to switch the counter on and off. Two other participants reported that the small visual display and the sequential procedure needed to store data on the card had caused them to make errors in recording over a 5-day period. However, there was acceptable agreement between the paper-based and counter repetitions record, with a correlation coefficient of  $r=0.86$  ( $p<0.001$ ) (Fig. 2).

None of the participants reported an adverse consequence from participation in the model training task.

<B>*Identification of the maximal tolerated dose*

For the model training task used in this design feasibility study, MTD was determined as 209 repetitions/day (Table 3).

<B>*Identification of the recommended Phase II dose*

Fig. 3 provides plots of the dose–response relationship in relation to: (a) the subjective report of number of repetitions; (b) the objective report of number of repetitions; and (c) the target repetitions. The best fit of data was found with a quadratic equation. Fig. 3 suggests that RPTD for the model training task used in this design feasibility study was approximately 160 repetitions/day.

## <A>Discussion

This dose-finding design was found to be feasible, and able to identify MTD and RPTD. However, pursuing dose finding on the basis of the current values is not directly applicable as the purpose of this study was to test the feasibility of the design, not to provide data to inform subsequent dose-ranging studies of the model training task as a potential intervention for future clinical practice. To do so would lead to false impressions that the dose parameters identified in this study are of relevance for application of clinical interventions to stroke survivors. The investigation reported here represents methodological development.

Strengths of the design tested are that the mFBS escalation procedure provided sufficient distance between doses, and the trial stopping rules avoided the provision of similar doses for different cohorts. However, requiring at least 10% difference in the number of repetitions between subsequent cohorts could have been too high. In detail, Cohort 4 were set 251 daily repetitions but this was not tolerable; as such, Cohort 5 were set 209 daily repetitions which was found to be tolerable. Following the escalation sequence, the subsequent dose would have been 237 daily repetitions but this was not >10% different from the intolerable 251. Therefore, a stopping rule was triggered and the study was stopped. Following the investigative design reported here, MTD was therefore set at 209 repetitions. However, it actually lies somewhere between 209 and 251 repetitions for the model training task. An MTD value between 209 and 251 is imprecise. Therefore, it could have been better to use a 5% difference between doses in the stopping rules.

The approach of identifying the dose of rehabilitation intervention before conducting clinical efficacy trials is uncommon [8,12,14]. Previous studies have mainly used dose-ranging designs with pre-specified doses with parallel groups [35] or intervention crossover [36]. The authors are only aware of one previous dose-finding study of a rehabilitation intervention, but a different design was used to that reported here [37]. Unlike the present study, the starting dose was relatively high (only two cohorts before MTD was found:  $n=6$ ), subsequent doses were not based on benefit as well as report of adverse consequences, each cohort received four different doses, de-escalation did not appear to have been considered and checking rules were not applied. Therefore, the earlier design only yielded MTD. No dose–response information was generated and therefore RPTD cannot be determined from the design used. Interestingly, the study reported here found that RPTD was 64% to 76% of MTD. In clinical practice, this represents a considerable resource saving compared with provision of MTD. Therefore, the design reported here may have advantages over that reported earlier [37].

A limitation of the current study was that problems were found with the counter used. Although this not a problem with the study design per se, it does mean that subsequent dose-finding studies need a better way of monitoring adherence to the target dose.

In any clinical research usage of the dose-finding design developed within this investigation, it will be important to ensure that participants are sufficiently homogeneous for the identified MTD and RPTD to be meaningful. However, for the methodological development investigation reported here, homogeneity in terms of, for example, time post stroke was not such a strong consideration. The principle that guided selection of participants for the present methodological investigation was that they were able to perform the model training task and had potential to benefit from it. Indeed, the participant selection criteria enabled the required testing of the dose-finding design for stroke rehabilitation research. The investigation reported here does not provide RPTD for subsequent use in stroke rehabilitation research or clinical practice. Rather, it provides an additional methodological tool to add to knowledge of stroke rehabilitation.



Although the final sample size of this investigation is relatively small compared with clinical efficacy trials, the number of participants (15) is within the range of 12 to 40 considered sufficient for pharmaceutical dose optimisation [25]. Regardless of the cohort size, it is important to follow a dose-escalation study with a dose-ranging study for confirmation of estimated dose before undertaking a clinical efficacy trial [20,38,39]. This would entail randomising participants to one of several doses around RPTD. Such dose-ranging studies have already been used in stroke rehabilitation research [35].

The next step for development of this dose-finding design is to test its application for identification of MTD and RPTD of task-orientated training for stroke survivors. Success is promised by a different form of dose escalation already conducted for exercise therapy [37].

*Ethical approval:* Ethical approval was in place before this study began (Reference ID: 14 EE 0005). All participants provided informed consent.

*Conflict of interest:* V. Pomeroy is an Associate Editor but was not involved in the review process for this article. The other authors declare no conflicts of interest.

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## Appendix 1

## Definitions of dose-finding elements used in this study

**Dose components**

Dose of exercise-based therapy is comprised of several components generally known as:

intensity (effort);

amount (quantity per session);

frequency (number of sessions per day); and

duration (number of weeks).

It is just as important to specify the levels of each component of exercise-based therapy as it is for constituents of a pharmaceutical compound. Not doing so restricts replication of research and transferability of research findings to clinical practice.

**Dose endpoints [16]**

The maximum tolerable dose is the highest dose at which adverse consequences are still acceptable for participants.

The minimum effective dose is the first dose with a clinically relevant effect that is significantly different from placebo.

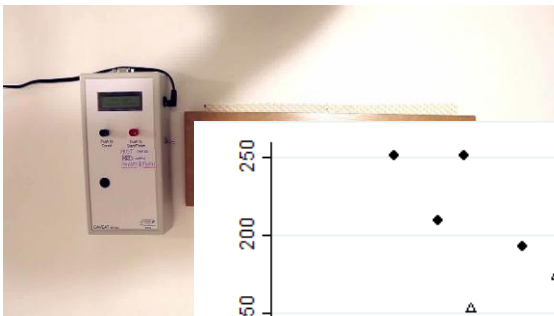
Recommended Phase II dose is that to be used in subsequent efficacy studies.



Fig 1. Flowchart to illustrate the dose-finding design. Tolerable dose is where two or more participants adhered to the set dose for that cohort and, at most, only one participant experienced an adverse consequence. Beneficial dose is where two or more participants demonstrated an increase of at least 10% in the outcome measure over the course of the training period.

Fig. 2. (a) Training task. Participants inserted fingers and thumb of paretic hand into the elastic band. They opened their hand to take the band from one tripod and place it on the other. This was one repetition. Next, extended fingers and thumb had to replace the band on the first tripod. After each repetition, the participant pressed the black button on the counter to provide a digital record. (b) Agreement between objective (OBM, counter) and subjective (SRM, paper-based) records of repetitions ( $r=0.86$ ,  $p<0.001$ ).

(a)



(b)

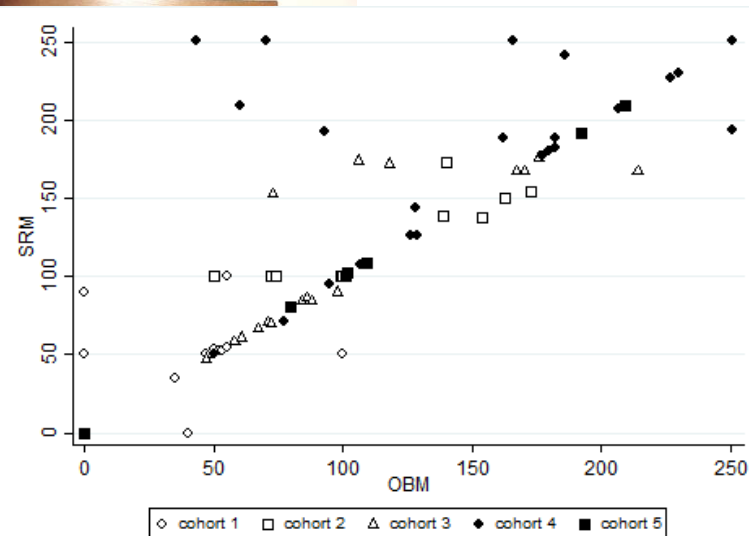
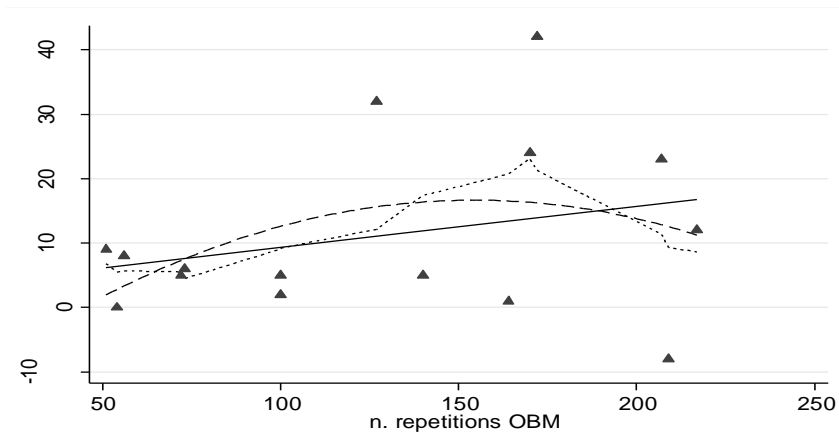




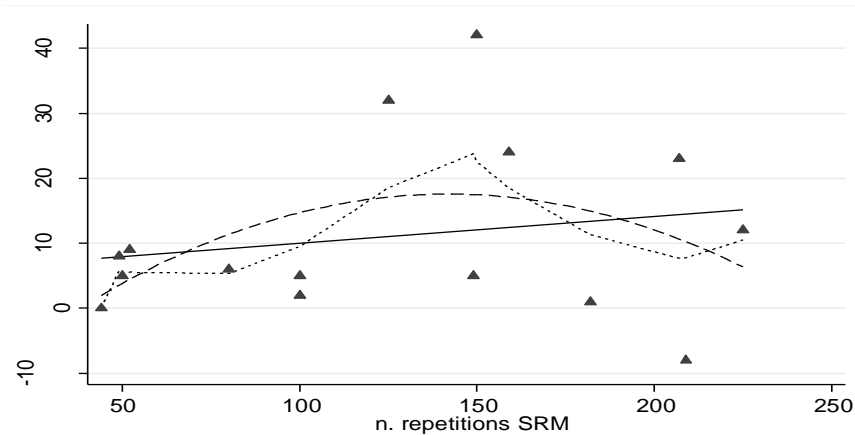
Fig.3. Dose–response relationships of primary outcome change from baseline (y-axis shows change in number of repetitions between pre- and post-training). (a) Dose–response relationships derived using the repetitions achieved recorded by the objective report of repetitions (OBM). Linear  $r^2 = 0.08$  and quadratic  $r^2 = 0.15$ . (b) Dose–response relationships derived using the subjective

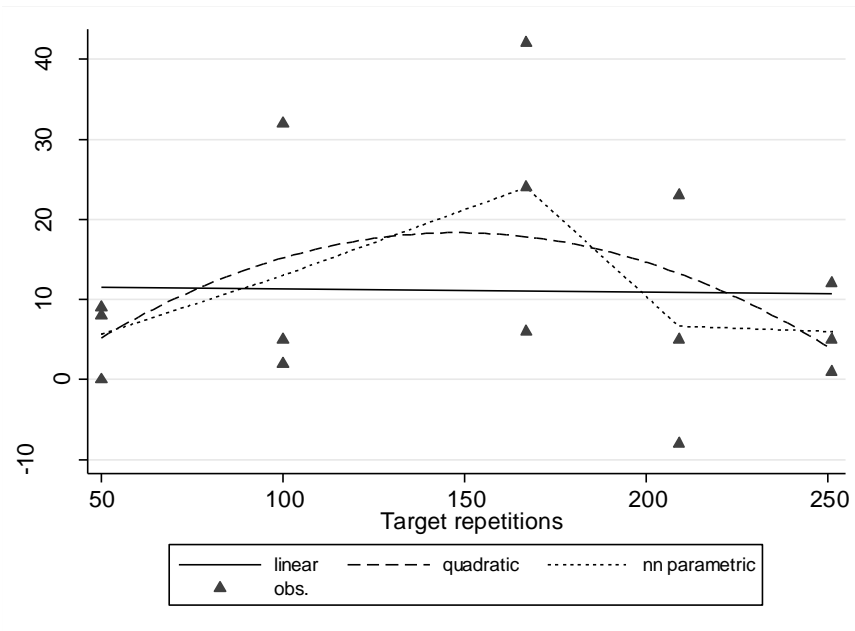
report of repetitions (SRM). Linear  $r^2 = 0.04$  and quadratic  $r^2 = 0.18$ . (c) Dose–response relationships derived using the target repetitions (assigned dose). Linear  $r^2 = 0.00$  and quadratic  $r^2 = 0.18$ . Triangles represent the participants' mean change in daily repetitions between pre- and post-training. The solid, dashed and dotted lines refer to the linear, quadratic and non-parametric mathematical models fitted to the data, respectively. The non-parametric curve is just a graphical gauge.

(a)



(b)





<captions for other figures are in file 'Figs 2 and 3'>

Table 1

Modified Fibonacci sequence (mFBS) dose escalation/de-escalation rules

Cohort	mFBS	Dose (D) increments
1	$D_1$	$D_1$
2	1.00	$2D_1$
3	0.67	$1.67D_2$
4	0.50	$1.5D_3$
5	0.40	$1.4D_4$
6	0.33	$1.33D_5$
7	0.33	$1.33D_6$
8+	0.33	$1.33D_{7+}$

Table 2

Participants' baseline characteristics and outcome scores by cohort

	All cohorts	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5
Baseline characteristics						
Age in years, mean (range)	68 (48 to 81)	69 (66 to 71)	72 (68 to 77)	63 (54 to 71)	60 (48 to 75)	74 (69 to 81)
Months post stroke, mean (range)	70 (9 to 289)	37 (9 to 67)	124 (18 to 289)	78 (12 to 120)	65 (11 to 156)	44 (30 to 54)
Dominant side affected, %	47	0	0	67	100	67
Female, %	47	67	0	33	100	33
Right side affected, %	33	0	33	67	0	67
Baseline scores, mean (SD)						
Max no. repetitions	23 (19)	17 (17)	25 (12)	25 (39)	17 (19)	33 (3)
Outcome scores, mean (SD)						
Max no. repetitions	34 (29)	23 (21)	38 (27)	49 (55)	23 (24)	15 (39)

SD, standard deviation; max, maximum.

Table 3  
 Individuals' adherence to target dose, per cohort, with decisions made on feasibility and efficacy as per primary outcome measure

Cohort	Participants	Target dose (repetitions)	Repetitions performed	Dose feasible	Primary outcome Max no. repetitions CanDo Digit Extend % change from baseline	Dose beneficial
	001		51		27	
1	002	50	54	Yes	0	Yes
	003		56		44	
	004		127		18	
2	005	100	100	Yes	91	Yes
	006		100		17	
	007		170		480	
3	008	167	172	Yes	61	Yes
	009		73		600	
	010		217		32	
4	011	251	163	No	100	NA
	012		140		36	
	013		209		14	
5	014	209	207	Yes	25	Yes
	015		72		77	

NA, not applicable.

**Box 1: Requirements for the model training task**

- Similarity with repetitive training used in experimental studies involving animal models.
- Relevant to task-specific training to enhance upper limb recovery after stroke.
- Performance parameters are recordable.
- Task challenging but achievable for each participant but with minimal variation.
- Can be undertaken in the home environment without the researcher present.
- Novel for most participants to minimise confounding effects of prior training.



