Received: 28 June 2022 | Revised: 11 October 2022 | Accepted: 23 October 2022

DOI: 10.1111/hae.14690

Haemophilia WFH WILEY

ORIGINAL ARTICLE

Muskuloskeletal

Proof of concept and feasibility of a blended physiotherapy intervention for persons with haemophilic arthropathy

Merel A. Timmer[1,2] | Isolde A. R. Kuijlaars[1] | Corelien Kloek[3,4] | Piet de Kleijn[1] | Roger E. G. Schutgens[1] | Cindy Veenhof[2,3] | Martijn F. Pisters[2,4,5]

[1]Van Creveldkliniek, Center for Benign Haematology, Thrombosis and Haemostasis, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[2]Physical Therapy Research, Department of Rehabilitation, Physical Therapy Science and Sport, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

[3]Research Group Innovation of Human Movement Care, University of Applied Sciences Utrecht, Utrecht, the Netherlands

[4]Center for Physical Therapy Research and Innovation in Primary Care, Julius Health Care Centers, Utrecht, the Netherlands

[5]Research Group Empowering Healthy Behaviour, Department of Health Innovations and Technology, Fontys University of Applied Sciences, Eindhoven, The Netherlands

Correspondence
Merel A Timmer, Van Creveldkliniek, Center for Benign Haematology, Thrombosis and Haemostasis, University Medical Center Utrecht, Utrecht University, The Netherlands; Physical Therapy Research, Department of Rehabilitation, Physical Therapy Science and Sport, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht University, the Netherlands.
Email: m.a.timmer@umcutrecht.nl

Abstract

Background: Regular physiotherapy with a physiotherapist experienced in the field is not feasible for many patients with haemophilia. We, therefore, developed a blended physiotherapy intervention for persons with haemophilic arthropathy (HA) (e-Exercise HA), integrating face-to-face physiotherapy with a smartphone application.

Aim: The aim of the study was to determine proof of concept of e- Exercise HA and to evaluate feasibility.

Methods: Proof of concept was evaluated by a single-case multiple baseline design. Physical activity (PA) was measured with an accelerometer during a baseline, intervention and post-intervention phase and analysed using visual inspection and a single case randomisation test. Changes in limitations in activities (Haemophilia Activities List [HAL]) and a General Perceived Effect (GPE) were evaluated between baseline (T0), post-intervention (T1) and 3 months post-intervention (T2) using Wilcoxson signed rank test. Feasibility was evaluated by the number of adverse events, attended sessions and open-ended questions.

Results: Nine patients with HA (90% severe, median age 57.5 (quartiles 50.5–63.3) and median HJHS 32 (quartiles 22–36)) were included. PA increased in two patients. HAL increased mean 15 (SD 9) points ($p = .001$) at T1, and decrease to mean +8 points (SD 7) ($p = .012$) at T2 compared to T0. At T1 and T2 8/9 participants scored a GPE > 3. Median 5 (range 4–7) face-to-face sessions were attended and a median 8 out of 12 information modules were viewed. No intervention-related bleeds were reported.

Conclusion: A blended physiotherapy intervention is feasible for persons with HA and the first indication of the effectiveness of the intervention in decreasing limitations in activities was observed.

KEYWORDS
blended care, e-health, exercise, haemophilia, physiotherapy

1 | INTRODUCTION

Haemophilia is a congenital disorder characterised by an increased risk of bleeding inside joints and muscles. Despite the introduction of prophylactic clotting factor replacement therapy, approximately two joint bleeds per year are still observed in patients with severe haemophilia who have access to prophylactic therapy.[1] Recurrent bleeding in a joint eventually causes haemophilic arthropathy (HA). Pathogenesis of HA is predominantly comparable to a degenerative joint disease like osteoarthritis (OA).[2] Clinical symptoms are pain, limited range of motion of the joint, and atrophy of surrounding muscles.[3] Consequently persons with HA experience limitations in activities and have a sedentary lifestyle more often than the general population.[4]

Exercise therapy, including resistance exercises, isometric exercises, bicycle ergometry, treadmill walking and hydrotherapy, seem to have a positive effect on several clinical outcomes, but a preferred exercise intervention for persons with HA is still undecided.[5–7] Additionally, physiotherapy is often not covered by health insurance and physiotherapists experienced with haemophilia are scarce. As a result, for many persons with HA regular and high-quality physiotherapy is insufficiently accessible. We, therefore, developed a blended physiotherapy intervention for persons with HA: e-Exercise HA.[8] Blended physiotherapy integrates face-to-face physiotherapy with a smartphone application.[9] It has the potential to support behavioural change and creates the opportunity to reach patients who have limited access to (specialised) physiotherapy. Furthermore, it could be used to support primary care physiotherapists, who are less experienced in treating persons with HA.

E-Exercise HA was built upon an effective blended physiotherapy intervention for persons with OA.[10] It was developed in co-creation with physiotherapists, patients, developers and researchers. The intervention consists of a) information modules for both patients and physiotherapists including text and videos, b) a graded activity program using a self-chosen activity and c) personalised video-supported exercises.[8] In patients with OA, increasing daily PA using a graded activity approach improves physical functioning.[11] As symptoms and pathogenesis of HA show parallels with OA, similar results are expected in HA.[2] In addition, e-Health applications have the potential to support behavioural change and therefore to contribute to a healthier movement behaviour.

The aim of the current study is to determine proof of concept of e-Exercise HA on improving physical functioning and increasing physical activity and to evaluate the feasibility of the intervention.

2 | METHODS

2.1 | Study design

Proof of concept of the e-Exercise HA intervention on physical activity (PA) and pain were evaluated by a randomised single-case multiple-baseline design.[12] This design enables testing hypotheses within subjects and allows for evaluation of variation in outcome over time. Figure 1 shows a graphical presentation of the design. Where regular intervention studies report only average effects, this design is particularly useful to test personalised interventions and understand mechanisms of action within individuals. Repeated observations, daily (PA) or with a 3 days interval (pain), were performed during a baseline phase (2–4 weeks), an experimental phase (12 weeks) and during a post-intervention phase (2–4 weeks). The baseline phase acts as a control and will therefore be compared to the intervention and post-intervention phase. By applying baselines of varying length observed effects of treatment can be distinguished from chance.[13] Effectiveness of the e-Exercise HA intervention on limitations in activities is evaluated with a pre-post design and a General Perceived Effect (GPE) score after finishing the intervention.

2.2 | Participants

Persons were eligible for inclusion if they were ≥18 years old, diagnosed with haemophilia, had HA in at least, but not limited to, one joint of the lower extremities (as low positive HJHS scores may not always be due to HA and in accordance with previous studies Pettersson score ≥3 points in one joint except from the item 'osteoporosis', Haemophilia Joint Health Score (HJHS) ≥2 points in one joint or HEAD-US ≥1 points in one joint for cartilage or bone abnormalities were considered HA[14,15]), reported limitations in activities (Haemophilia Activities List (HAL) <95) and had a personal activity goal. Exclusion criteria were patients <1 years after joint

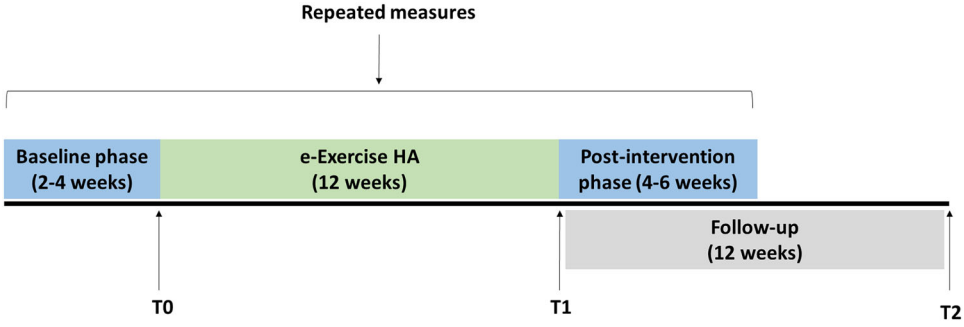


FIGURE 1 Graphical presentation of the study design.

replacement or arthrodesis, <6 weeks after a joint or muscle bleed in the lower extremity and patients with active synovitis in the lower extremity.

2.3 | Procedure

Between April 2019 and September 2020 patients at the van Creveldkliniek were informed about the study by flyers and an information screen in the waiting room and information in the newsletter of the clinic. Persons with haemophilia (PWH) who visited the physiotherapist at the clinic and were eligible for inclusion were personally approached. The intervention was started after informed consent was obtained. The research protocol was approved by the Institutional Review Board of the University Medical Center Utrecht, the Netherlands (protocol number: 18–81/C). The intervention was performed by a single experienced physiotherapist (MT) related to the Haemophilia Treatment Center. During the first visit, the personal goal of the patient was established using the Canadian Occupation Performance Measure (COPM). The electronic data capture system 'Castor' was used to automatically send the repeated measures and pre- and post-intervention questionnaires by email.

2.4 | Intervention

The 12 weeks e-Exercise intervention integrates face-to-face physiotherapy and a smartphone application. Physiotherapists create for each patient a personal account on a website. Through this account, the physiotherapist can generate and personalise an exercise program for each patient, monitor his progress and adapt the treatment program according to individual needs. Patients are able to review their personal program through a personal account within a smartphone app. The intervention consists of a) weekly self-management information modules b) a behavioural graded activity approach directed at increasing the duration of a self-chosen activity in a time-contingent way and c) personalised exercises supported with texts and videos. Within face-to-face sessions, physiotherapists can start the exercise program, choose an activity goal and choose exercises and parameters. Further on, they can recall online self-management modules and discuss how the themes affect the patient's personal situation. When needed, the graded activity program and the prescribed exercises can be adjusted. The number and the timing of the visits depend on personal needs of the patient. The intervention is described in more detail in a previous publication.[8]

2.5 | Outcome measures

Demographic characteristics were collected including: age, type of haemophilia, severity, baseline joint status (HJHS) and personal activity goal.

2.5.1 | Repeated measures

PA was assessed with the Activ8 accelerometer, worn in the pocket of the trousers.[16] The Activ8 has been validated and distinguishes between six postures and activities: lying down, sitting, standing, walking, running and cycling.[17–19] Participants were asked to wear the Activ8 every day during the baseline, the intervention and the post-intervention phase. The activity that best matched with the activity chosen for the graded activity module was used as an outcome measure. The number of hours spend on the chosen activity was calculated per day.

Pain intensity was assessed using the Numerical Rating Scale (NRS).[20] The NRS is an 11-point rating scale ranging from 0 to 10 points. A score of 0 represents 'no pain', 10 represents 'worst pain possible'. Patients indicated the number that corresponds to their maximum pain level in the past day. The NRS is considered a valid and reliable instrument to measure pain. Pain was measured every 3 days, using an automatically send an email with the NRS.

Patient-specific activity limitations were measured with the Patient Specific Functioning Scale (PSFS), which is considered reliable and valid in several musculoskeletal disorders.[21,22] The PSFS is an 11-point rating scale ranging from 0 to 10 points. A score of 0 represents 'no limitations' and a score of 10 represents 'impossible to perform'. Every 3 days, participants were asked to indicate the extent of limitations they experienced with the chosen activity in the last 24 h using automatically send emails.

2.5.2 | Pre- and post-intervention measures

Self-perceived limitations in activities were measured with the component score 'lower extremity basic' of the HAL. The HAL is a validated and reliable 42-item haemophilia-specific self-administered questionnaire assessing self-perceived limitations in activities in three component scores; upper extremity, lower extremity basic and lower extremity complex.[23,24] As the lower extremity basic component score includes items like standing and walking on different surfaces, it is considered to fit best with the intervention and the population. Self-reported limitations in activities were assessed at baseline, after the intervention and at 12 weeks follow-up. In addition, self- perceived change in physical functioning was assessed using a 7 -point General Perceived Effect (GPE) scale (0 = very much worse, 3 = no change, 6 = very much better).[25] GPE was evaluated after the intervention and at 12 weeks follow-up. Questionnaires were automatically sent by email.

2.5.3 | Feasibility and other measures

Feasibility of the intervention was assessed by the number of adverse events (bleeding episodes), the number of online modules accessed and the number of face-to-face meetings attended. Satisfaction with

the intervention was evaluated with open-ended questions (What did you think of the online application/the face-to-face visits/the information modules/the graded activity module/the exercises/the pop-up messages? Do you have any other feedback?)

2.6 | Data analysis

Statistical analyses were performed using R studio version 3.5.1. with the packages 'ggplot2' and 'SCRT'.[26,27] Descriptive results were presented as medians and interquartile ranges or means and standard deviations for changes scores. Changes in PA, pain, patient specific limitations in chosen activity (repeated measures data) were evaluated using visual inspection and a single case randomisation test. Visual inspection was performed by creating plots including the mean and bands of 2*standard deviation (SD) calculated from the baseline phase. Visual plots can be used to give insight into the mechanism of effect. Two or more successive data points in the intervention phase or the post-intervention phase that fall outside the bandwidth of 2SD are generally considered significant change. However, in order to improve reliability and accuracy, it is recommended to use a statistical test as well. The single case randomisation test is used as a second test to determine whether the null hypothesis 'there is no change in outcome between the baseline phase and the intervention phase' should be rejected. The single case randomisation test determines whether the obtained responses are the same as those that would have been obtained under any other random ordering. Missing repeated measures data was handled by linear regressing adjacent data points either side of the missing data. If missing data within a case exceeded 50% in the intervention phase or less than 3 data points were available in the baseline phase, the case could not be analysed. For pre- and post-intervention comparison the nonparametric Wilcoxson signed rank test was used, as the sample size is small. *p*-values <.05 were considered statistically significant.

3 | RESULTS

A total of 10 persons with HA were included in the study; all suffered from severe haemophilia. Median age of the participants was 57.5 years (IQR 50.5–63.3). Clinical characteristics of the participants are shown in Table 1. One participant had to stop during the baseline phase due to COVID-19 restrictions and did not restart afterwards.

TABLE 1 Clinical characteristics of the participants

	Median (IQR) or *n* (%)
Age	57.5 (50.5–63.3)
Severe	9 (90)
Haemophilia A	7 (70)
Joint status (HJHS)	32 (22–36)

Abbreviation: HJHS, Hemophilia Joint Health Score.

The personal goal of 8/9 participants was to increase walking duration to 30 or 60 min. One participant had the goal to increase cycling duration with moderate e-bike support to 90 min. Personalised exercises that were prescribed included functional walking exercises and stability exercises, choices were made based on baseline functional ability and personal goals. All prescribed exercises are listed in Appendix 1.

3.1 | Repeated measures

3.1.1 | Physical activity

A total of four participants had no missing PA data, four other participants had between 2% and 16% missing data. For one participant (p2) PA data of the baseline phase was completely missing due to malfunction of the Activ8 and could therefore not be analysed. Randomisation tests confirm a significant increase in PA in p3 and p10. The other participants showed no change in PA. Plots of a participant without significant change in PA (p1) and a participant with a significant increase in PA (p10) are shown respectively in Figure 2. A complete overview of PA plots of all participants is presented in Appendix 2.

3.1.2 | Pain

A total of four participants had no missing pain scores, two other participants had 22% and 23% missing data in the intervention phase and had >3 data points in the baseline phase available and were therefore included in the analysis. For three participants pain scores could not be analysed since they had >50% missing data in the intervention phase (P5 and P8) or had less than 3 data points in the baseline phase (p9). Visual inspection of the plots presenting pain intensity shows a slight decrease in pain in 2 participants (p6 and p10). Randomisation tests confirm only a significant difference in p10 ($p = .03$). Visual plots of pain scores are shown in Figure 3 for p1 and p10, respectively. A complete overview of visual plots of the pain scores of all participants is presented in Appendix 3.

3.1.3 | Patient specific activity limitations

Missing data for patient-specific activity limitations were the same as for pain scores, as they were assessed on the same electronic form. Visual inspection and randomisations tests did not show any changes in patient specific limitations. A visual plot of patient-specific limitations of participant 10 is presented in Figure 4.

3.2 | Pre- and post-test measures

Pre- and post-measures of perceived limitations in activities and perceived effect of the intervention are presented in Table 2. At baseline participants scored a median of 33 points (quartiles 25–50) on the HAL.

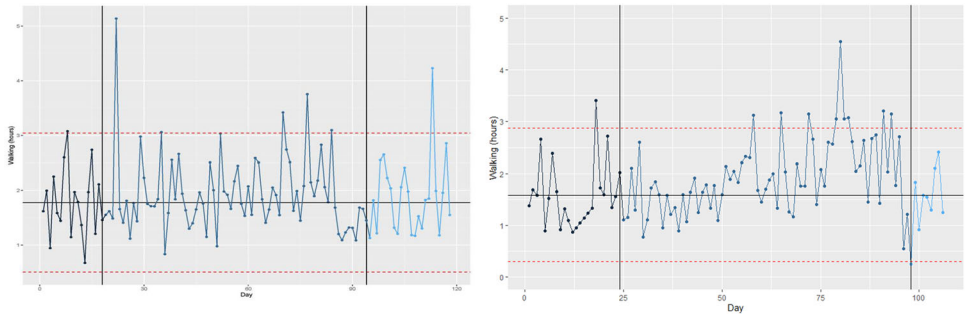


FIGURE 2 Hours per day spend in the chosen activity (walking) for participant 1 and 10.
* Vertical lines present the transition from baseline phase to intervention phase, and intervention phase to post intervention phase.
* The black horizontal line represents the mean of the baseline phase.
* The dotted red lines represent +/−2 SD from the mean of the baseline phase.

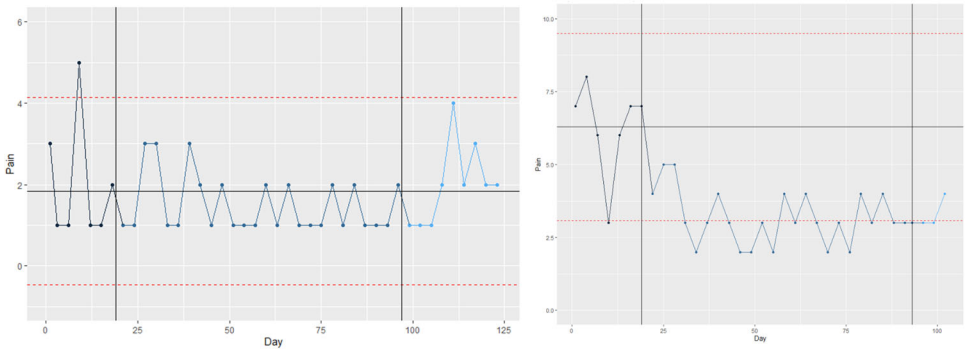


FIGURE 3 Numerical Pain Scores per 3 days for participant 1 and 10.
* Vertical lines present the transition from baseline phase to intervention phase, and intervention phase to post intervention phase.
* The black horizontal line represents the mean of the baseline phase.
* The dotted red lines represent +/−2 SD from the mean of the baseline phase.

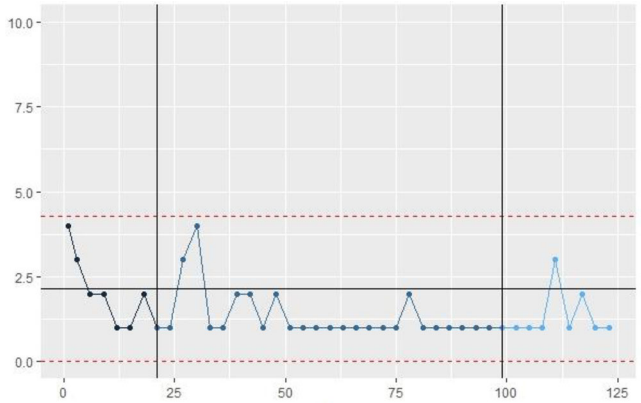


FIGURE 4 Patient specific activity limitations per 3 days for participant 10.
* Vertical lines present the transition from baseline phase to intervention phase, and intervention phase to post intervention phase.
* The black horizontal line represents the mean of the baseline phase.
* The dotted red lines represent +/−2 SD from the mean of the baseline phase.

HAL scores increased between baseline and post intervention with a mean of 15 points (SD 9; $p = .001$), indicating less limitations in activities. At 3 months post intervention HAL scores were mean 8 (SD 7; $p = .012$) points higher compared to baseline. At both post intervention measures 8/9 participants indicated an improvement (score >3) on general perceived effect.

3.3 | Feasibility

Participants attended median 5 (range 4–7) face-to-face sessions and viewed median 8 out of 12 information modules. One elbow bleed, unrelated to the intervention, was reported. Open ended questions showed that participants appreciated the personalised approach of the intervention, enabling more face-to-face sessions when needed and less when not needed (all). The face-to-face sessions were a motivation to adhere to the program or used to ask additional questions (P8, P9, P10). Pop up messages with reminders to perform exercises and activities improved adherence according to two participants, the

TABLE 2 Pre- and post-measures of perceived limitations in activities and perceived effect

	HAL lower basic							GPE	
PID	T0	T1	T2	ΔHAL T1-T0	*p*-value T1-T0	ΔHAL T2-T0	*p*-value T2-T0	T1	T2
1	33	50	43	17		10		5	5
2	33	40	–	7		–		4	4
3	43	60	40	17		−3		4	4
4	20	53	40	33		20		2	5
5	73	77	83	4		10		5	5
6	30	53	36	23		6		5	5
7	Stop in BL	–	–	–		–		–	–
8	43	50	57	7		14		5	5
9	57	70	60	13		3		5	4
10	20	33	26	13		6		4	2[a]
Total	33 (25–50)	53 (45–65)	42 (37–59)	15 (9)	.001	8 (7)	.012		

Total scores are presented as median (quartiles) or mean (SD); significance testing based on Wilcoxson signed rank test.
Abbreviations: BL, baseline; GPE, Global perceived effect (0 = very much worse, 3 = no change, 6 = very much better); HAL, Haemophilia Activity List; T0, start baseline; T1, end intervention; T2, 12 weeks after ending the intervention.
[a]Measurement 1 week after hospital admission for not haemophilia related problem.

others turned them off as it annoyed them. Although most participants did already know most information from the information modules, they still found it useful to refresh their memory (P3, P4, P5, P8, P9). The graded activity approach surprised participants in their own ability to increase walking or cycling distance when distance is increased gradually (P5, P8), although discipline is needed in order to stick to the program (P1, P4). Some participants found it very helpful to have the smartphone application with their personalised program and video-supported exercises (P1, P10), others did not use the application very consistently. Improvements proposed by the participants are to include abilities to track performance like step count, walking/cycling distance, speed and routes (P8, P9, P10).

4 | DISCUSSION

The current study shows a positive general perceived effect of e-Exercise HA and a decrease in perceived limitation in basic activities of the lower extremities. An increase in PA was only seen in two participants and only one participant experienced a significant decrease in pain. In contrast to the decrease in perceived limitations in basic activities of the lower extremities measured pre- and post-intervention using the HAL, repeated measures of limitations with the chosen activity (PSFS) did not change. As the intervention used a graded activity approach, the increasing duration of the chosen activity could explain why the perceived limitations with the chosen activity did not decrease during the intervention. The intervention can be considered safe, as it did not result in any adverse events. Patients with HA considered the blended intervention feasible and appreciated the personal and blended approach.

4.1 | Comparison with literature

The results of the current study, are in accordance with a previous systematic review showing that exercise interventions for persons with haemophilia are safe and feasible.[5] Most included studies found positive results concerning effectiveness of exercise interventions, comparable to the current study. However, previous studies only used outcomes on the level of body functions. Patient reported outcomes and outcomes on the level of activities and participation are rarely used. Only one previous study included a functional outcome (walking distance) and none used a patient reported outcome.[28] Patient reported outcomes on the level of activities and participation are more relevant for patients and it is known that they only slightly correlate with body functions.[29] In addition, most previous interventions include classic strength, coordination and/or flexibility exercises, in contrast to self-management information modules, a graded activity approach and functional exercises in the current study. One previous study investigated functional treadmill training and found an increase in muscle strength.[30] Only one online exercise intervention for persons with haemophilia was previously developed, however, effectiveness was not yet investigated.[31] Similar to the current intervention, the e-Exercise osteoarthritis intervention on which the current intervention was based showed subject improvement on physical functioning and no change in objectively measured physical activity. Results of the e-Exercise osteoarthritis intervention were comparable to the usual physiotherapy group. The lack of improvement in objectively measured physical activity is in accordance with a meta-analysis of behavioural physical activity interventions in lower limb OA. This may indicate that additional or adjusted components are needed to improve physical activity.

4.2 | Strengths and limitations

A strength of this study is that the repeated measures design enables us to evaluate the course of and variation in outcome over time. Instead of analysing an average effect, it facilitates the understanding of the mechanisms of action. To evaluate the effect of the intervention on PA, choices had to be made in how to operationalise PA (e.g., time spend walking, step count, time spend in moderate to vigorous PA). In a previous study we propose analysing movement behaviour patterns, including the whole spectrum of movement behaviour. Movement behaviour can be considered the combination of daytime sedentary behaviour physical activity (with low, moderate and high intensity) and sleep. However, within the repeated measures design evaluating movement behaviour patterns was not feasible. It was therefore decided to analyse the activity closest to the activity chosen by the patient within the graded activity approach. As only two participants show an increase in time spend in the chosen activity, changes in other parameters of PA are not expected.

Both the repeated measures design and the pre-post design enabled us to use the participant as its own control. During the baseline phase patients were allowed to receive any kind of treatment, including pain medication, orthotics and physiotherapy treatment at the patient's own initiative. This can therefore be considered usual care. We can thus conclude that the intervention is more effective than usual care. A second advantage of the chosen repeated measures design is that it is particularly suitable for small samples. Power of the repeated measures design is determined by the number of repeated measures within a person. For the pre- post-intervention comparison, the sample size was small. Nevertheless, differences were large enough to determine that they were significant. The sample size does however limit generalisability. Younger patients and patients with less advanced HA are relatively underrepresented in the current study, in addition all patients had access to prophylactic clotting factor replacement therapy. Generalising the results of this study to younger patients, with less advanced HA or patients without access to prophylactic therapy must therefore be done with caution.

4.3 | Clinical implication and future research

Physiotherapists could decide to use a blended exercise strategy, like e-Exercise HA, to treat persons with haemophilia. It could be very suitable for patients who live far form a clinic, have a busy schedule and/or have high self-management skills. Furthermore, it is recommended to include a goal-oriented approach like graded activity in future exercise interventions for persons with HA, as patients particularly valued this part.

As the intervention did not improve PA in most patients, further development of the intervention should focus on strategies to improve PA. This is in accordance with the feedback from the participants, who propose to include abilities to track performance like step count, walking/cycling distance, speed and routes. As in the current study the intervention was performed by a physiotherapist experienced with haemophilia, future studies should evaluate whether this blended physiotherapy approach can support primary care physiotherapists in the treatment of persons with HA. In future evaluative studies outcomes like adherence and coping could be included as well.

5 | CONCLUSION

A blended physiotherapy intervention including self-management information modules, a graded activity approach and personalised exercises (e-Exercise HA) is feasible for persons with HA. The current study shows a first indication of effectiveness of the intervention in decreasing limitation in activities. Future research should focus on the development of elements that improve PA as well as evaluating the intervention in primary care.

AUTHOR CONTRIBUTIONS

CJJK, CV, and MFP developed the previous e-Exercise programs and used their experience to advise on the development of e-Exercise HA. MAT and MFP designed the research study. MAT and IARK performed data collection. MAT analysed the data and wrote the manuscript. All authors contributed to the interpretation of the data, critical reviewing and editing of the manuscript. All authors approved the final manuscript.

ACKNOWLEDGEMENTS

This study was supported by an unrestricted research grant from Pfizer (ID 35384245). The institutional review board of the University Medical Center Utrecht (reference number 18–081/c) provided ethical approval and the ethics protocol reference number.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Ahnstrom J, Berntorp E, Lindvall K, Bjorkman S. A 6-year follow-up of dosing, coagulation factor levels and bleedings in relation to joint status in the prophylactic treatment of haemophilia. *Haemophilia*. 2004;10(6):689-697.
2. Roosendaal G, van Rinsum AC, Vianen ME, van den Berg HM, Lafeber FP, Bijlsma JW. Haemophilic arthropathy resembles degenerative rather than inflammatory joint disease. *Histopathology*. 1999;34(2):144-153.
3. Timmer MA, Pisters MF, de KP, de Bie RA, Fischer K, Schutgens RE. Differentiating between signs of intra-articular joint bleeding and chronic arthropathy in haemophilia: a narrative review of the literature. *Haemophilia*. 2015;21(3):289-296.
4. Timmer MA, Pisters MF, de Kleijn P, de Bie RA, Schutgens REG, Veenhof C. Movement behaviour in adults with haemophilia compared to healthy adults. *Haemophilia*. 2018;24(3):445-451.
5. Strike K, Mulder K, Michael R. Exercise for haemophilia. *Cochrane Database Syst Rev*. 2016;12:CD011180.
6. Bladen M, Carroll L, Dodd C, et al. Results of feasibility and safety of randomised controlled trial of a musculoskeletal exercise intervention versus usual care for children with haemophilia. *Haemophilia*. 2020;26(5):e223.

7. Siqueira TC, Dominski FH, Andrade A. Effects of exercise in people with haemophilia: an umbrella review of systematic reviews and meta-analyses. *Haemophilia*. 2019;25(6):928-937.
8. Timmer MA, Kloek CJJ, de Kleijn P, et al. A blended physiotherapy intervention for persons with hemophilic arthropathy: development study. *J Med Internet Res*. 2020;22(6):e16631.
9. Bossen D, Kloek C, Snippe HW, Dekker J, de Bakker D, Veenhof C. A blended intervention for patients with knee and hip osteoarthritis in the physical therapy practice: development and a pilot study. *JMIR Res Protoc*. 2016;5(1):e32.
10. Kloek CJJ, Bossen D, Spreeuwenberg PM, Dekker J, de Bakker DH, Veenhof C. Effectiveness of a blended physical therapist intervention in people with hip osteoarthritis, knee osteoarthritis, or both: a cluster-randomized controlled trial. *Phys Therap*. 2018;98(7):560-570.
11. Pisters MF, Veenhof C, de Bakker DH, Schellevis FG, Dekker J. Behavioural graded activity results in better exercise adherence and more physical activity than usual care in people with osteoarthritis: a cluster-randomised trial. *J Physiother*. 2010;56(1):41-47.
12. Bulte I, Onghena P. An R package for single-case randomization tests. *Behav Res Methods*. 2008;40(2):467-478.
13. Hoogeboom TJ, Kwakkenbos L, Rietveld L, den Broeder AA, de Bie RA, van den Ende CH. Feasibility and potential effectiveness of a non-pharmacological multidisciplinary care programme for persons with generalised osteoarthritis: a randomised, multiple-baseline single-case study. *BMJ Open*. 2012;2(4).
14. Timmer MA, Foppen W, Schutgens RE, Pisters MF, Fischer K. Comparing findings of routine haemophilia joint health score and haemophlia early arthropathy detection with ultrasound assessments in adults with haemophilia. *Haemophilia*. 2017;23(2):e141.
15. St-Louis J, Abad A, Funk S, et al. The hemophilia joint health score version 2.1 validation in adult patients study: a multicenter international study. *Res Pract Thromb Haemost*. 2022;6(2):e12690.
16. Activ8. VitaMove. p. https://www.activ8all.com/product/activ-professional-activity-monitor/
17. Fanchamps MHJ, Horemans HLD, Ribbers GM, Stam HJ, Bussmann JBJ. The accuracy of the detection of body postures and movements using a physical activity monitor in people after a stroke. *Sensors (Basel)*. 2018;18(7):2167.
18. Lankhorst K, van den Berg-Emons RJ, Bussmann JBJ, Horemans HLD, de Groot JF. A novel tool for quantifying and promoting physical activity in youths with typical development and youths who are ambulatory and have motor disability. *Phys Ther*. 2019;99(3):354-363.
19. Validation of the Active8 Activity Monitor: detection of body postures and movements. University Medical Center Rotterdam; 2013.
20. Hawker GA, Mian S, Kendzerska T, FrenchM. Measures of adult pain: visual analog scale for pain (VAS pain), numeric rating scale for pain (NRS pain), McGill pain questionnaire (MPQ), short-form McGill pain questionnaire (SF-MPQ), chronic pain grade scale (CPGS), short form-36 bodily pain scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP). *Arthritis Care Res (Hoboken)*. 2011:S240-S252.
21. Chatman AB, Hyams SP, Neel JM, et al. The patient-specific functional scale: measurement properties in patients with knee dysfunction. *Phys Ther*. 1997;77(8):820-829.
22. Westaway MD, Stratford PW, Binkley JM. The patient-specific functional scale: validation of its use in persons with neck dysfunction. *J Orthop Sports Phys Ther*. 1998;27(5):331-338.
23. van Genderen FR, Westers P, Heijnen L, et al. Measuring patients' perceptions on their functional abilities: validation of the haemophilia activities list. *Haemophilia*. 2006;12(1):36-46.
24. Kuijlaars IAR, van Emst M, van der Net J, Timmer MA, Fischer K. Assessing the test-retest reliability and smallest detectable change of the haemophilia activities list. *Haemophilia*. 2021;27(1):108-112.
25. Kamper SJ, Ostelo RW, Knol DL, Maher CG, de Vet HC, Hancock MJ. Global perceived effect scales provided reliable assessments of health transition in people with musculoskeletal disorders, but ratings are strongly influenced by current status. *J Clin Epidemiol*. 2010;63(7):e1.
26. Bulte I, Onghena P. Randomization tests for multiple-baseline designs: an extension of the SCRT-R package. *Behav Res Methods*. 2009;41(2):477-485.
27. Team RC. *R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing*, 2016.
28. Eid MIM, Aly SM. Effect of resistance and aerobic exercises on bone mineral density, muscle strength and functional ability in children with hemophilia. *Egypt J Med Hum Genet*. (15):139-147.
29. Fischer K, Nijdam A, Holmstrom M, et al. Evaluating outcome of prophylaxis in haemophilia: objective and self-reported instruments should be combined. *Haemophilia*. 2016;22:80-86.
30. Abd-Elmonem AMAA, Elnaggar RK. Effect of treadmill training on quadriceps and hamstring muscles strength in children with knee haemoarthrosis. *Int J Physiotherap Res*. 2014;2(4):581-588.
31. Wagner B, Seuser A, Kruger S, et al. Establishing an online physical exercise program for people with hemophilia. *Wien Klin Wochenschr*. 2019;131(21-22):558-566.

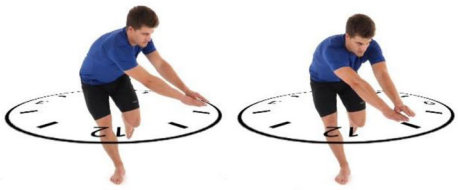
How to cite this article: Timmer MA, Kuijlaars IAR, Kloek C, de Kleijn P, et al. Proof of concept and feasibility of a blended physiotherapy intervention for persons with haemophilic arthropathy. *Haemophilia*. 2023;29:290–307. https://doi.org/10.1111/hae.14690

APPENDIX 1

Marching on the spot

Slow march with arm swing

Proprioception clock

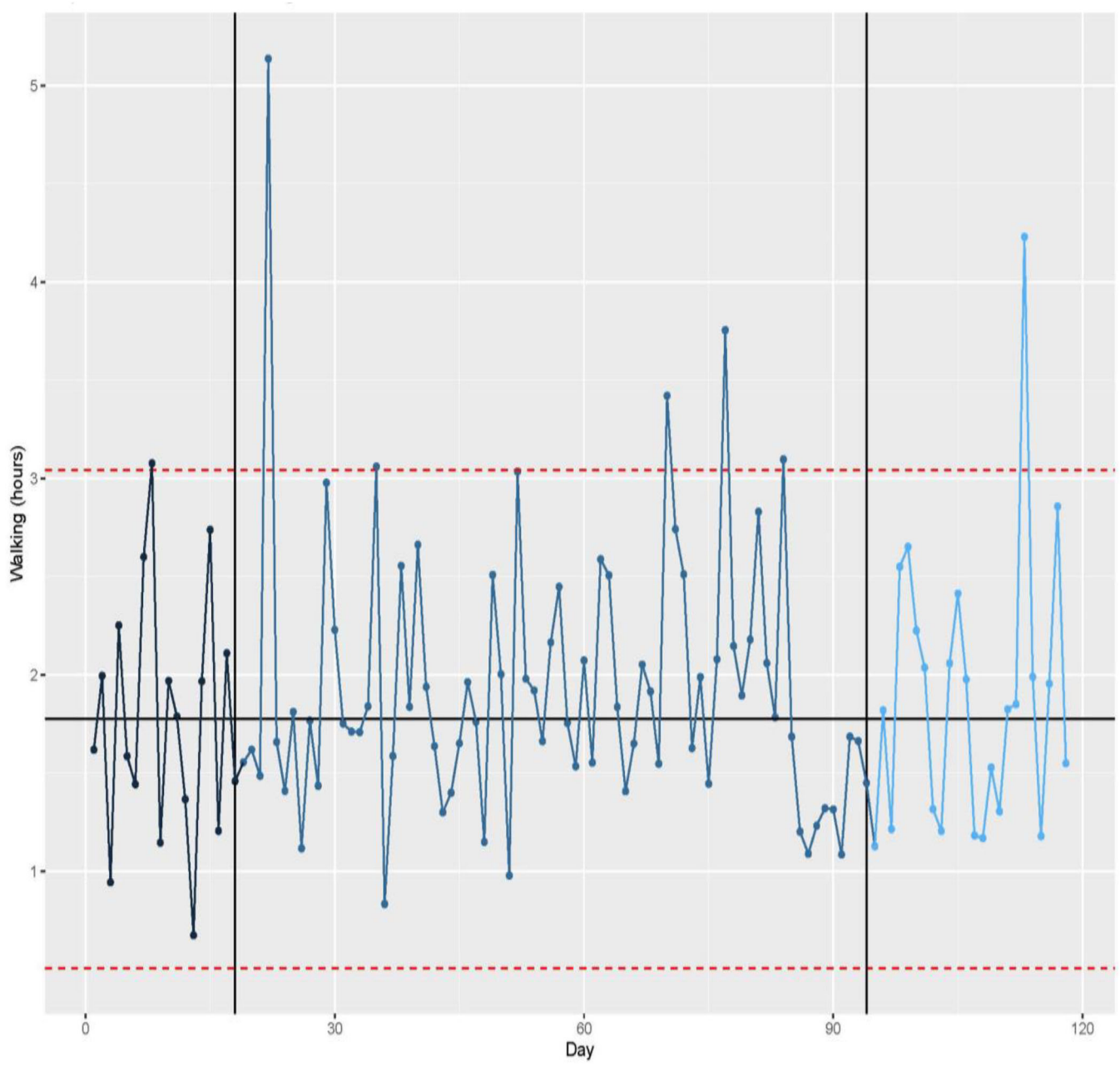


Proprioception clock upperbody

Forward step up with support

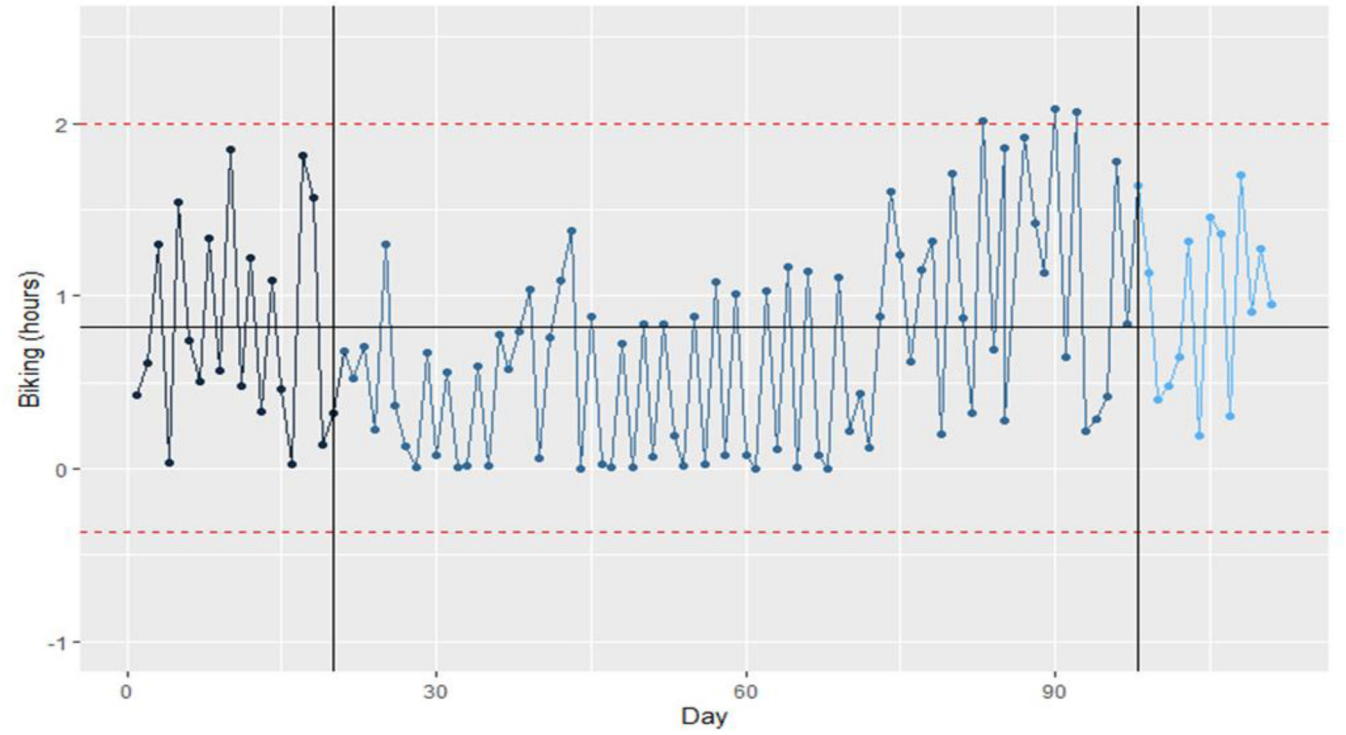
Forward step up

APPENDIX 2

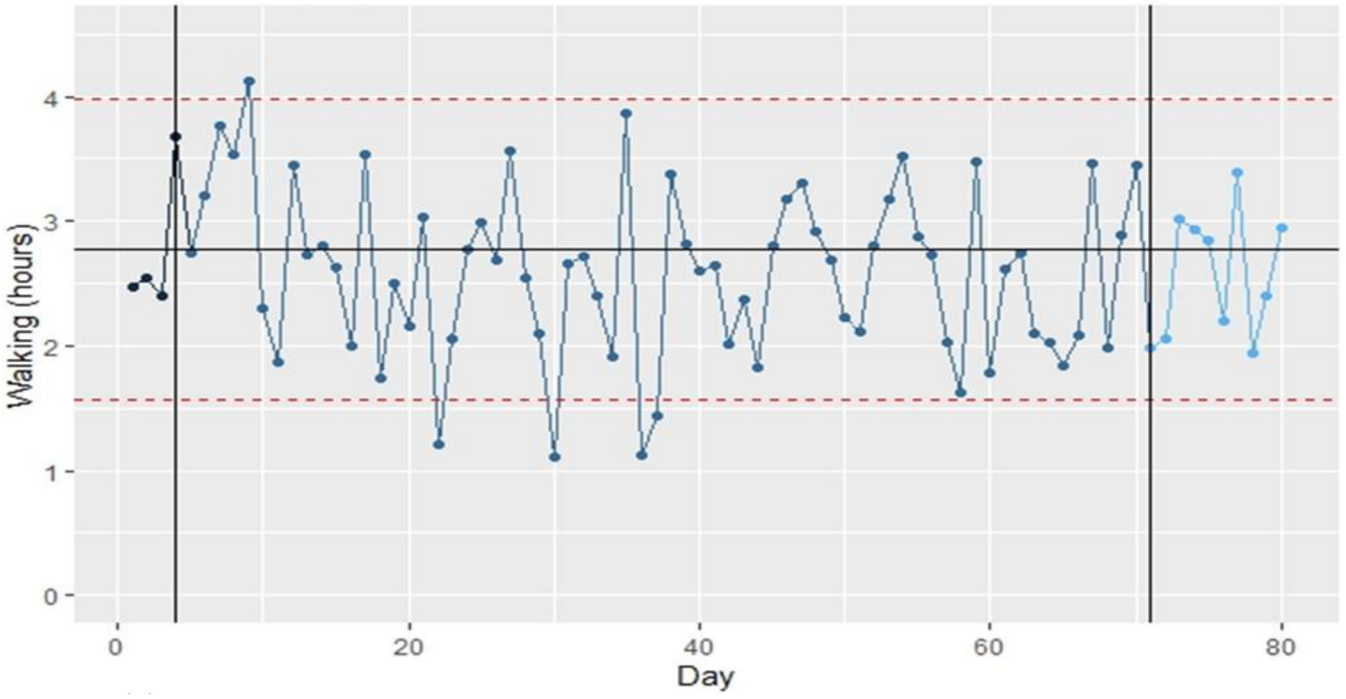


Participant 1

Participant 2 – not enough data available



Participant 3



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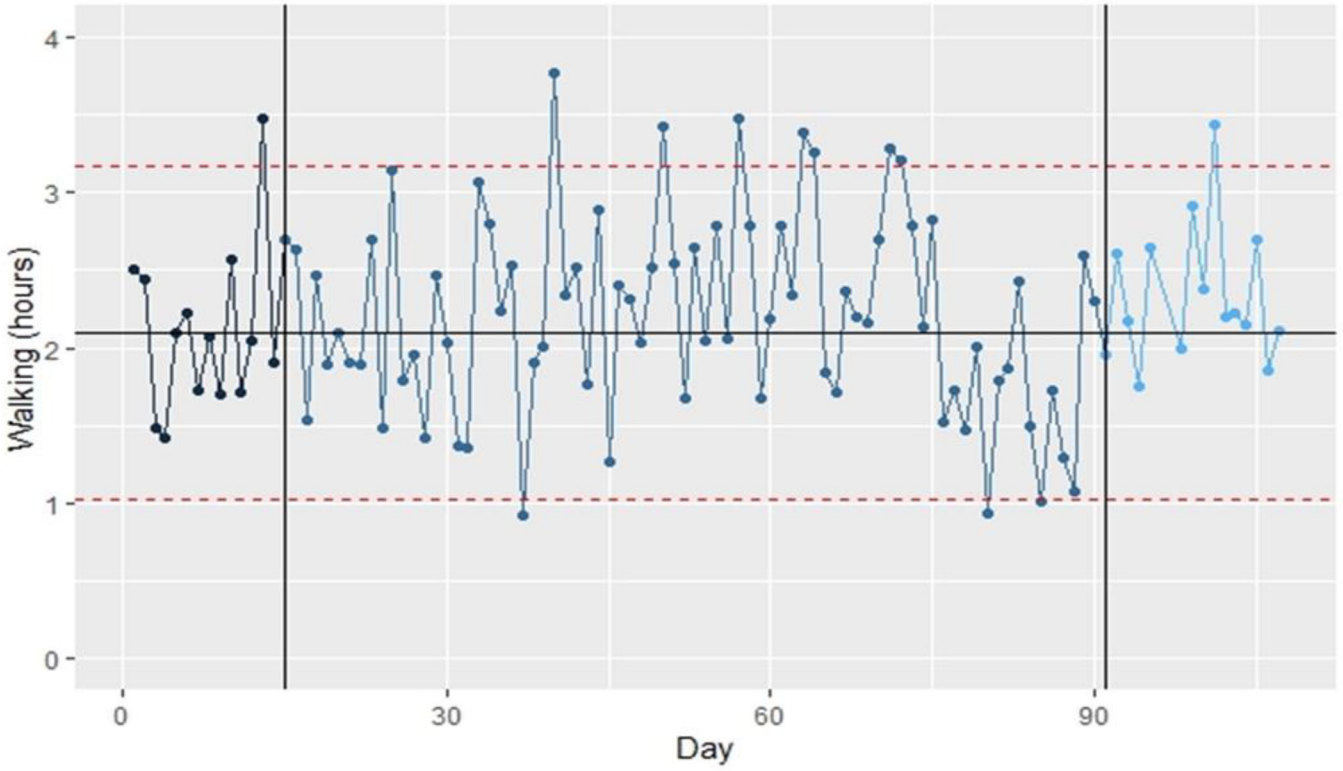

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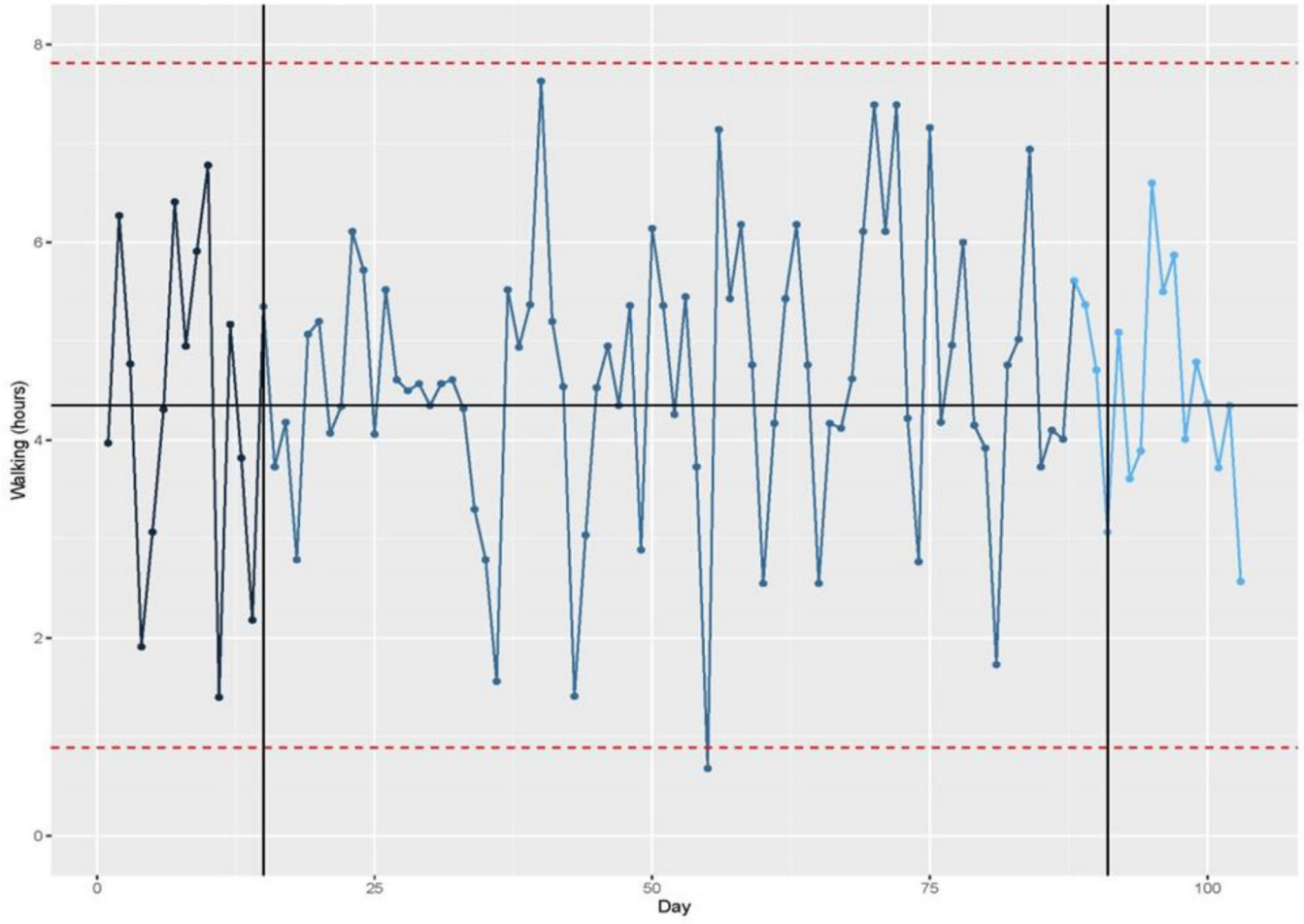
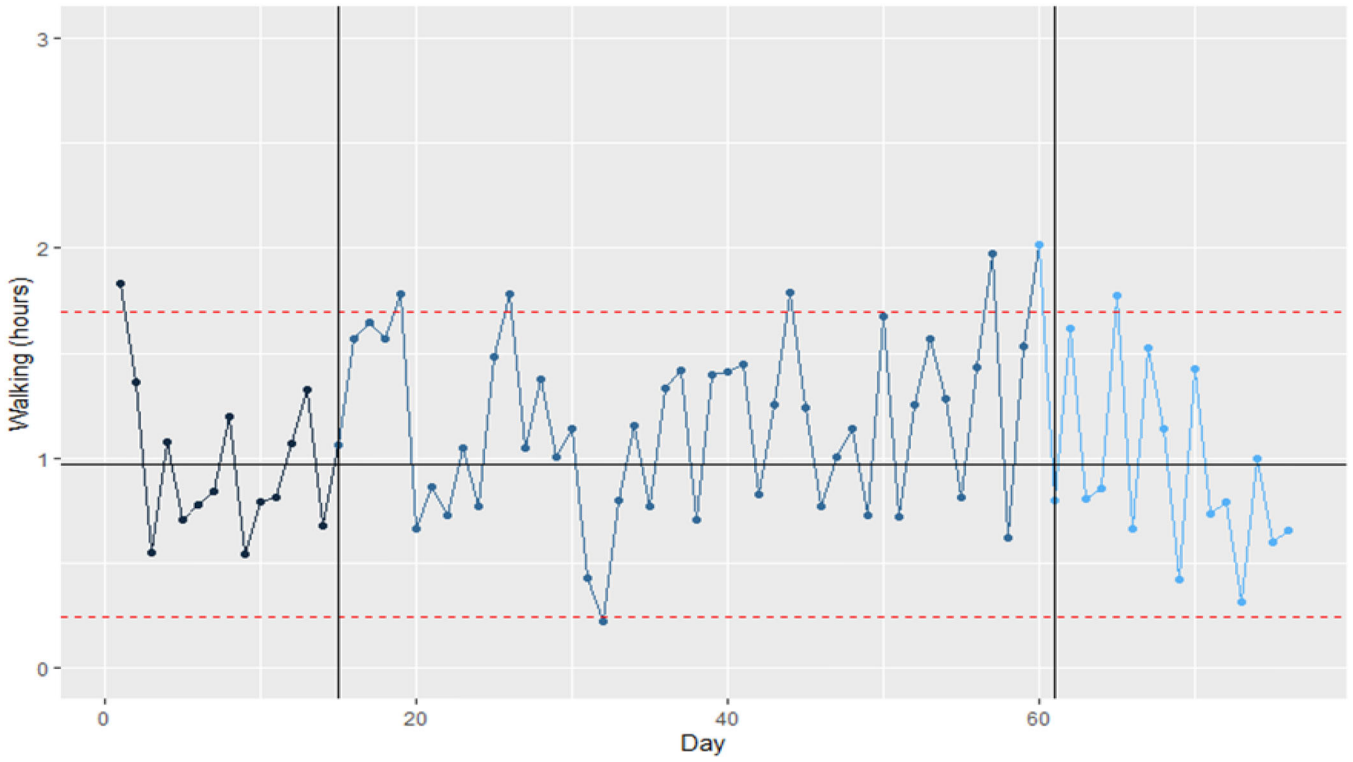


Participant 6

Participant 7 – stopped in baseline phase



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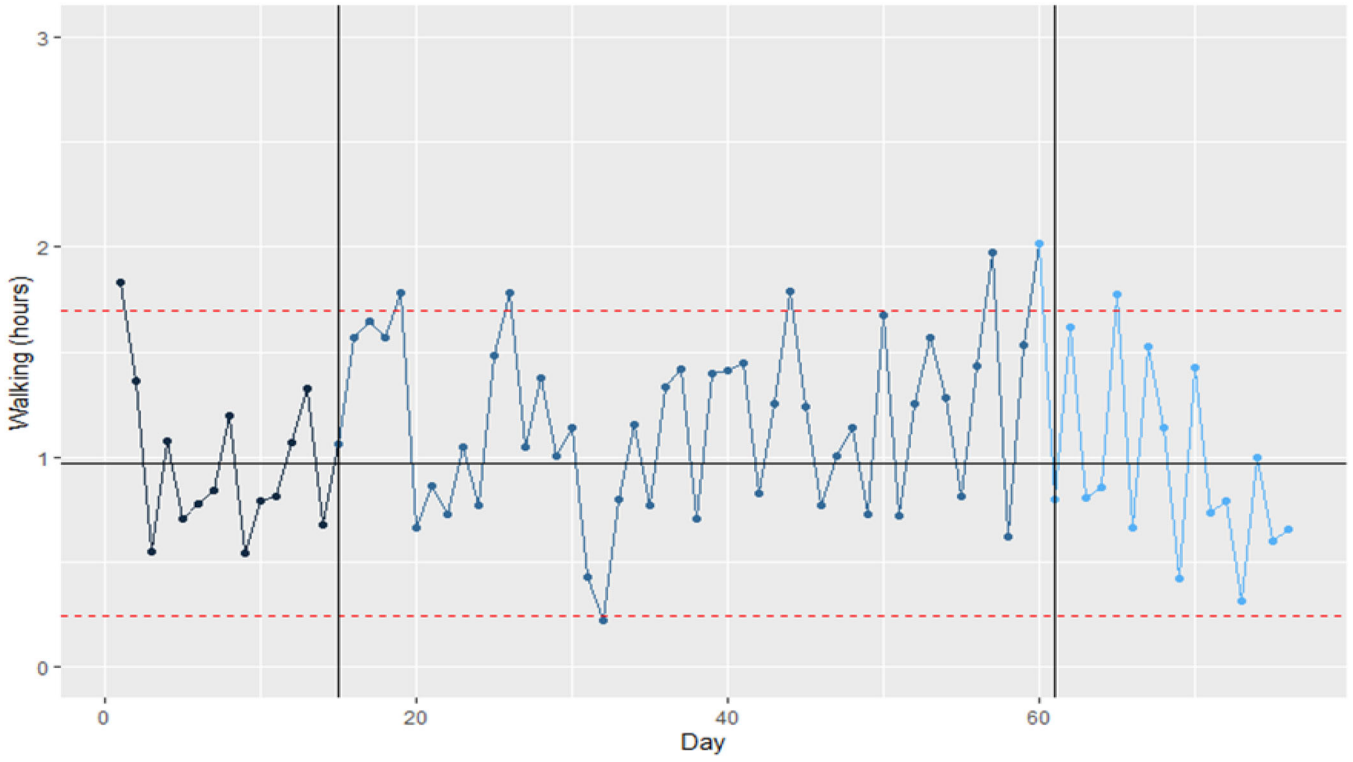
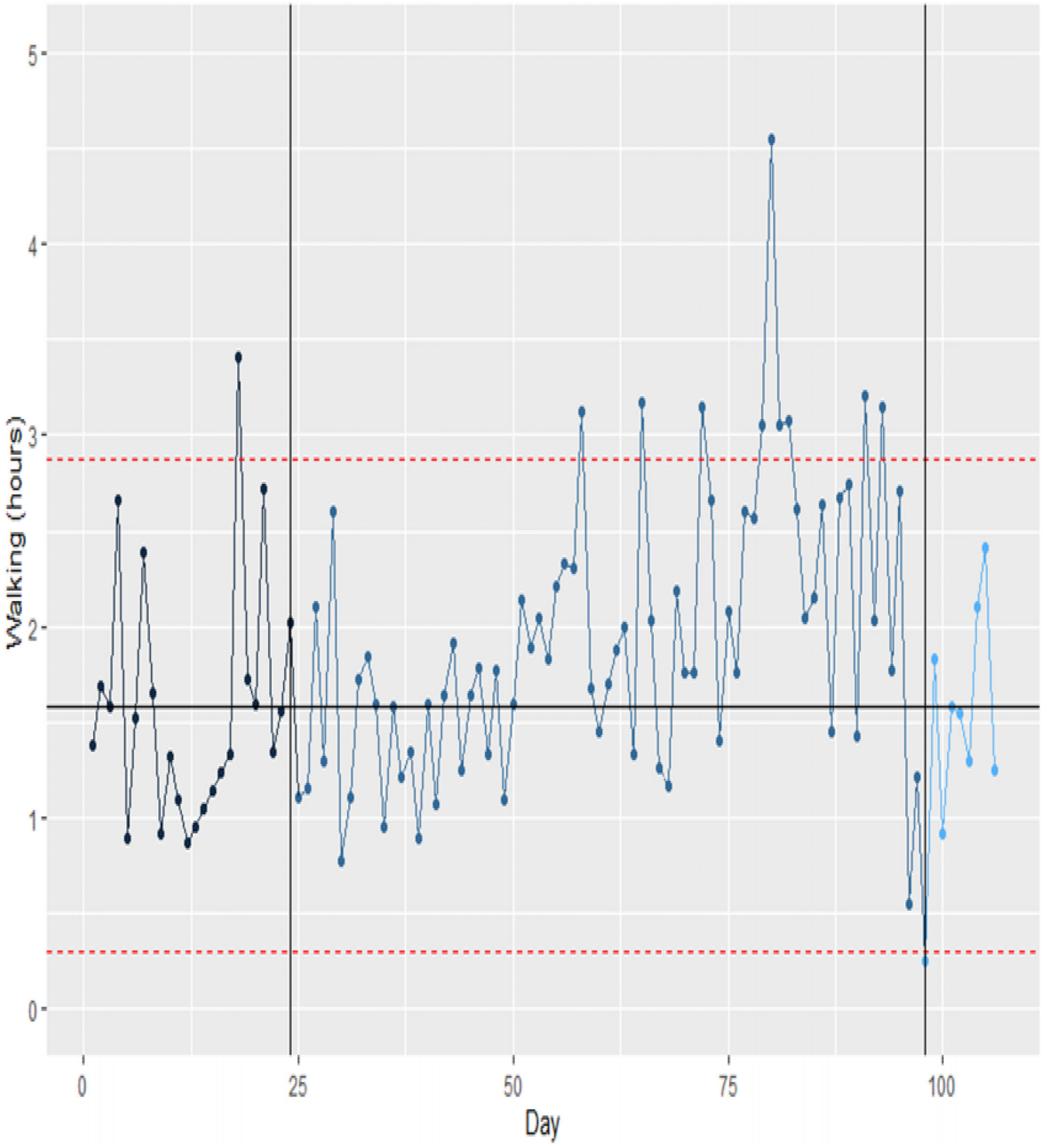
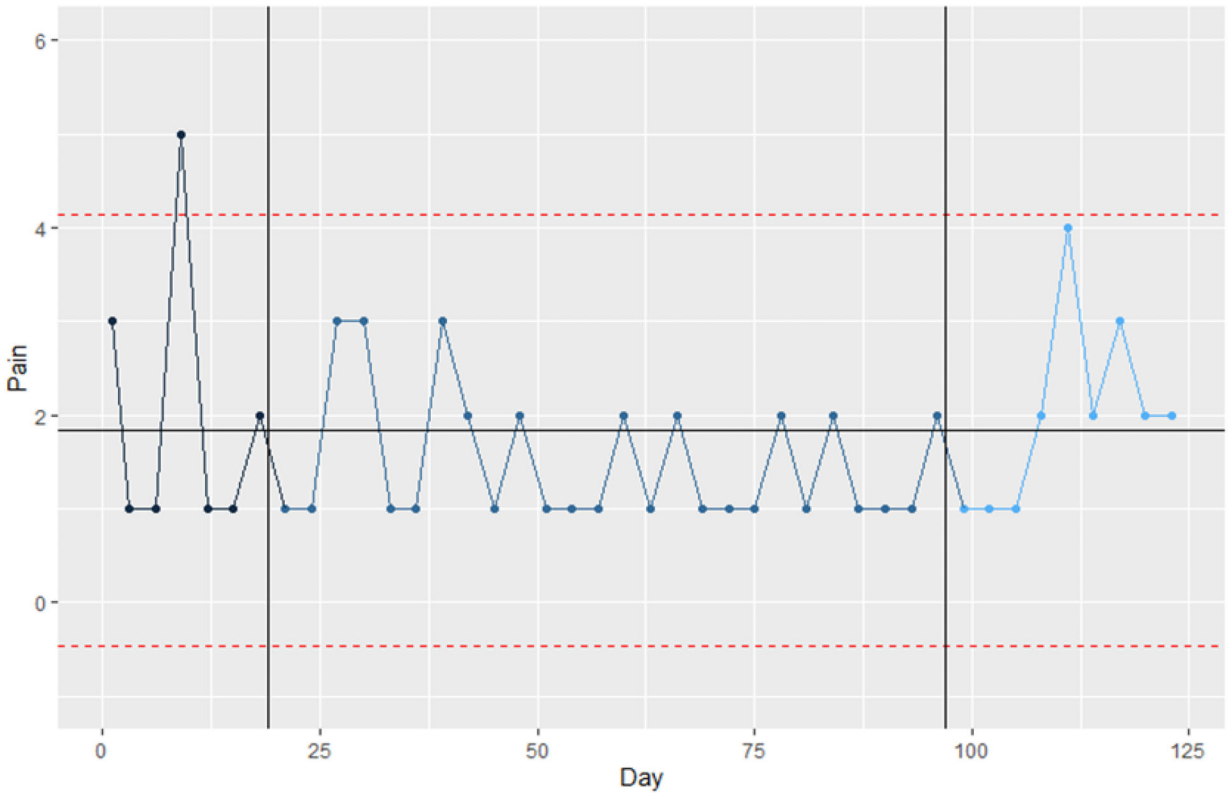


Participant 9

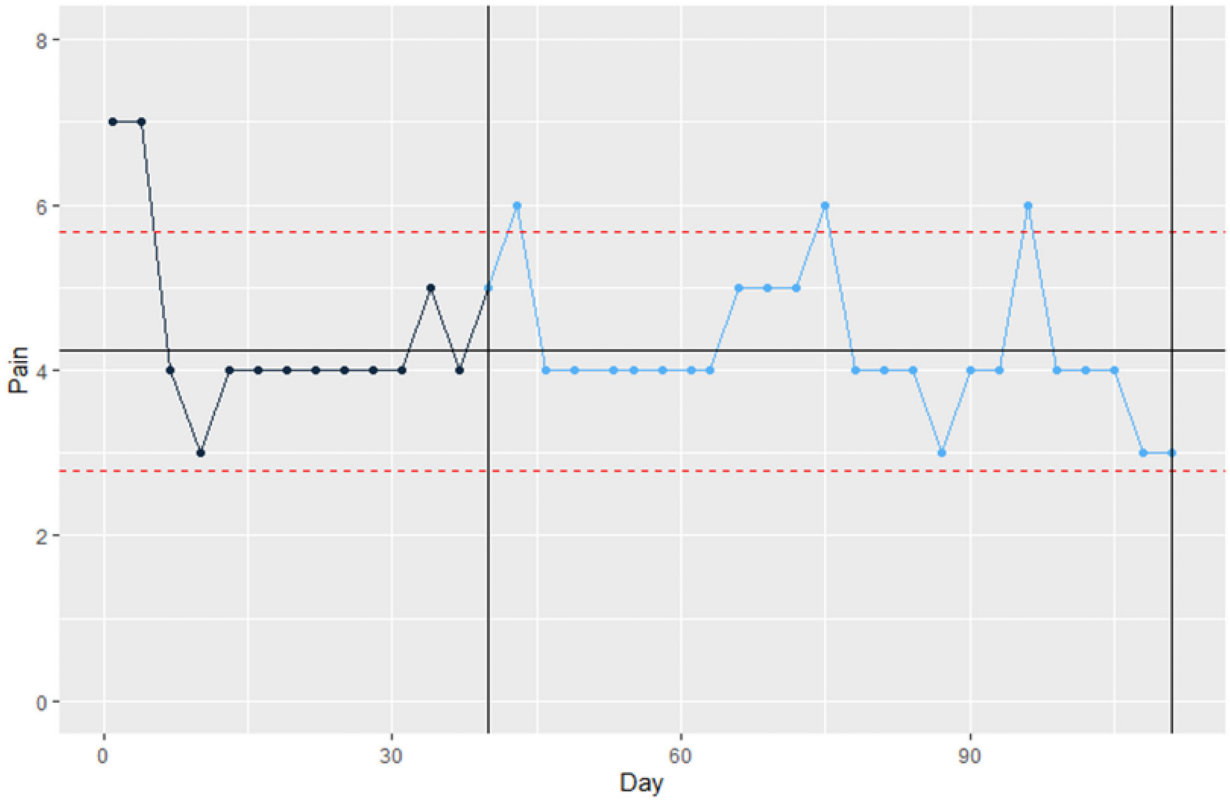


Participant 10

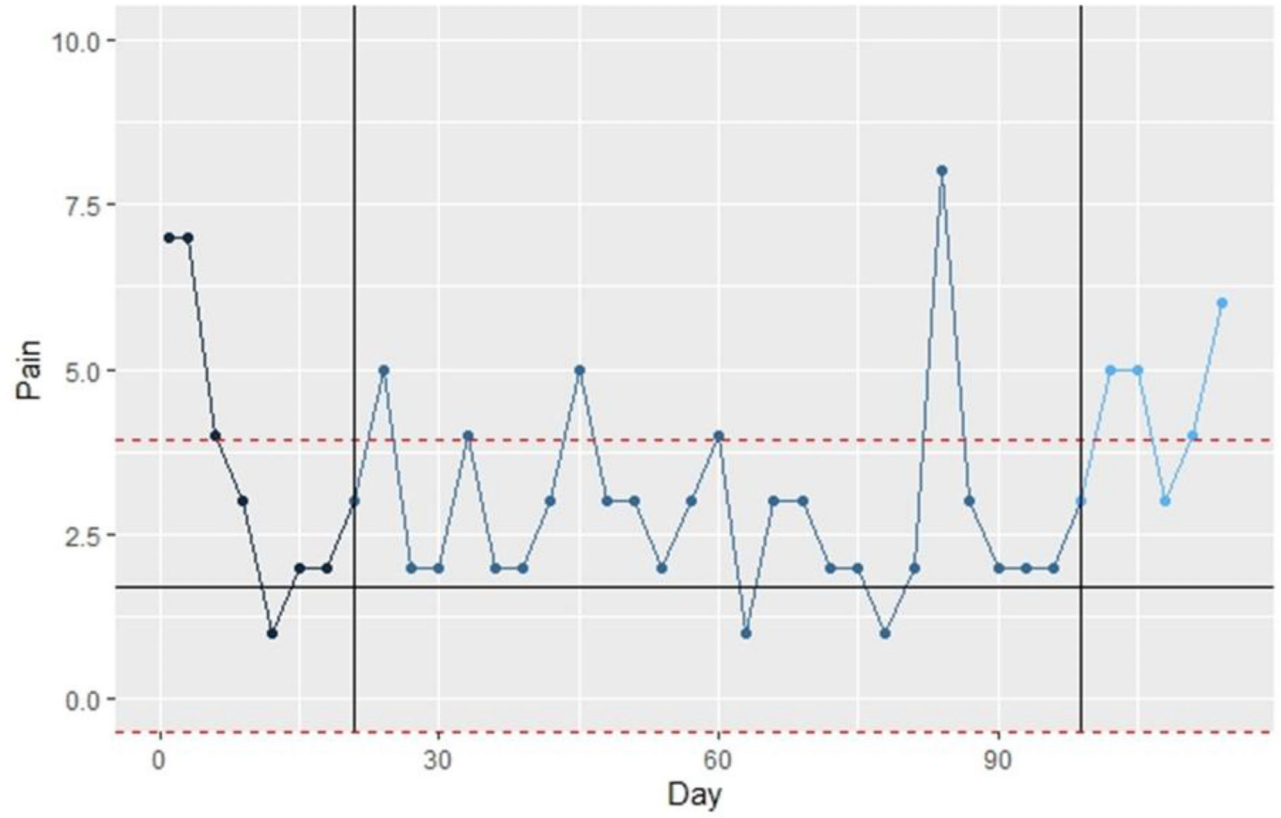
APPENDIX 3



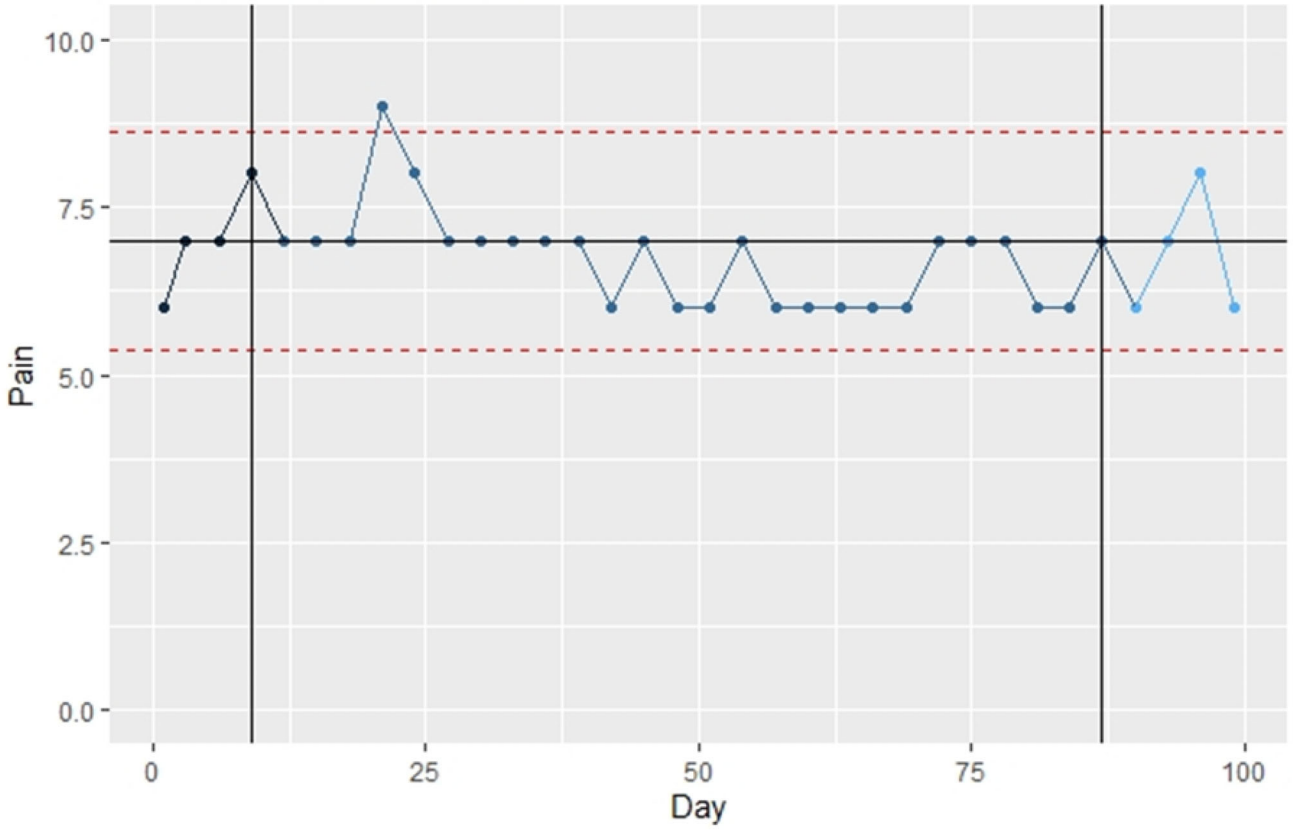
Participant 1



Participant 2

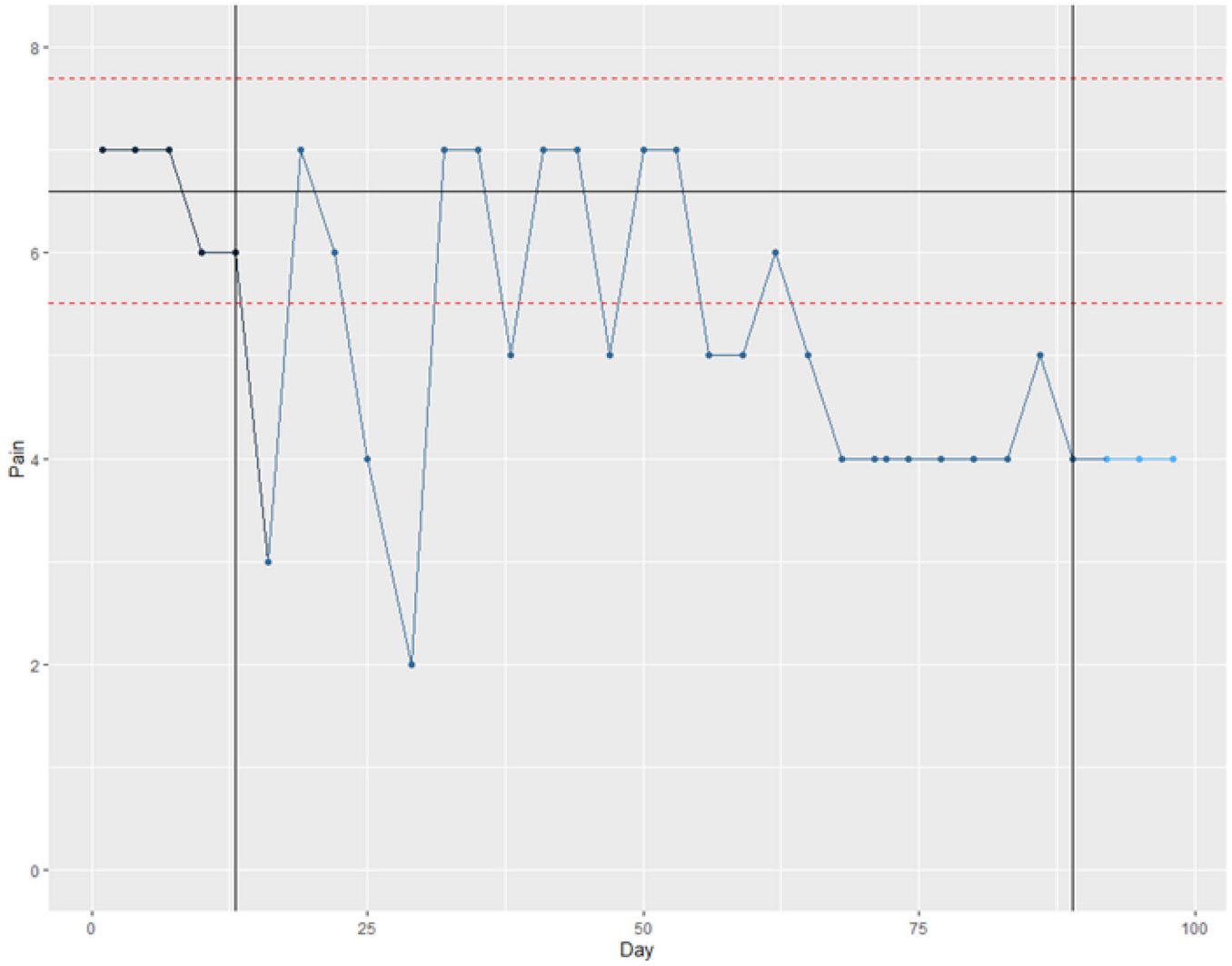


Participant 3



Participant 4

Participant 5 – no pain scores available

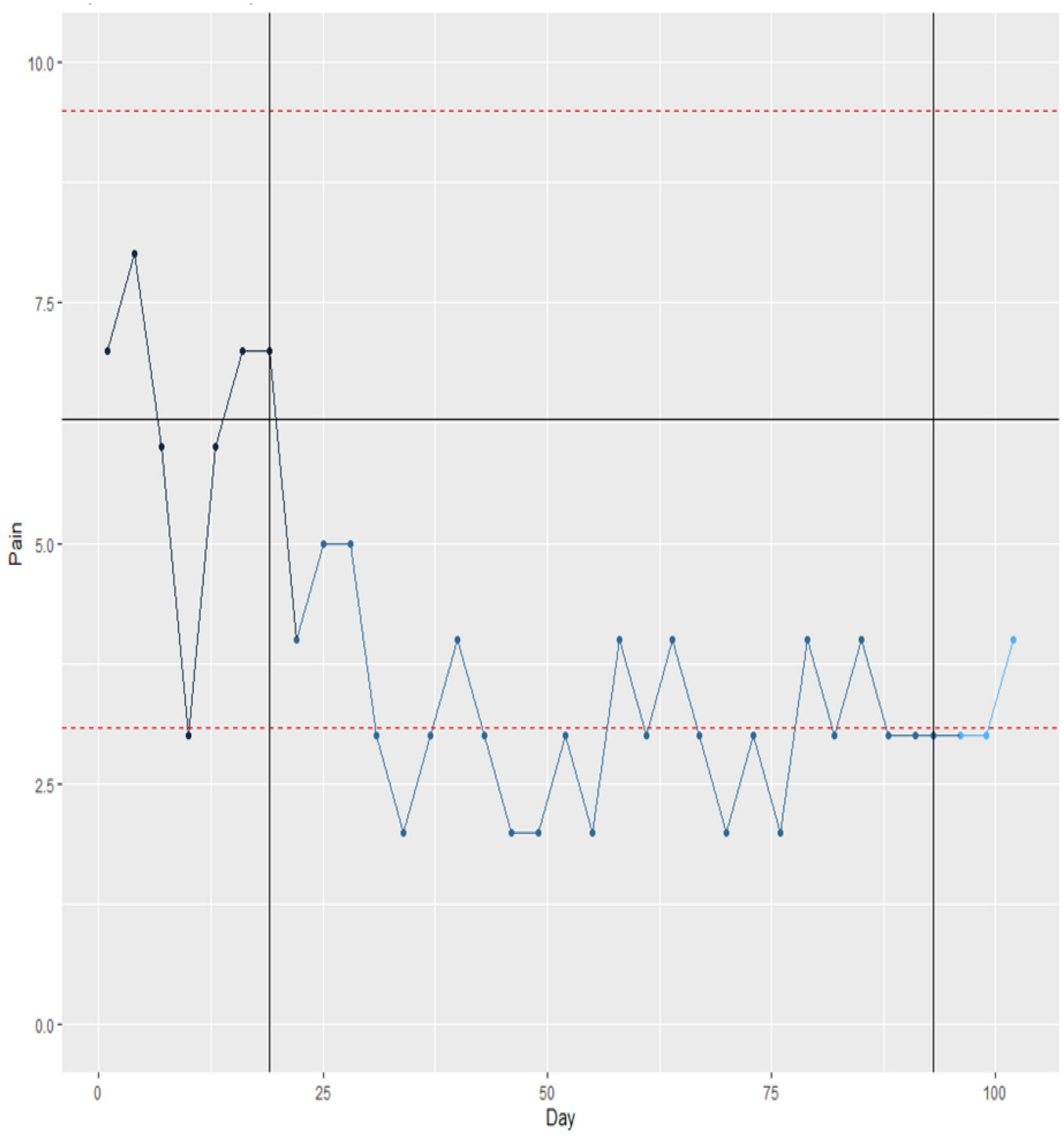


Participant 6

Participant 7 – Stopped in baseline phase

Participant 8 – not enough data available

Participant 9 – not enough data available



Participant 10