Statistical analysis plan (SAP) for the (cost-)effectiveness of:

an innovative, personalised intervention of therapeutic VirtuAl Reality (VR) IntEgrated within physioTherapY for a subgroup of complex chronic low back pain (CLBP) patients (VARIETY-study)

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Study objectives and outcomes

Main objective

- To evaluate the effectiveness of physiotherapy with integrated multimodal VR for patients with complex CLBP, compared to usual primary physiotherapy care on physical functioning evaluated by the Oswestry Disability Index (ODI) at 3 months (primary end-point) and 12 months follow-up.

Secondary objective

- To evaluate the effectiveness of physiotherapy with integrated multimodal VR for patients with complex CLBP, compared to usual primary physiotherapy care on secondary outcome measures pain intensity, pain related fears, pain self-efficacy, physical activity level, global perceived effect and problems with activities at 3 months (primary end-point) and 12 months follow-up.

- To evaluate the cost-effectiveness of physiotherapy with integrated multimodal VR for patients with complex CLBP, compared to usual primary physiotherapy care for the 12-month period.

Trial methods

Design

- This study is a pragmatic, multicenter, two-arm, parallel, superiority, cluster-randomized controlled trial. Outcome variables will be measured at baseline, after 1 month (T1; during treatment), 3 months (T3; directly post-treatment), 6 months (T6; 3 months post-treatment) and 12 months (T12; 9 months post-treatment) follow-up, as described in table 1.

Randomization

- Eligible physiotherapists will be randomized on practice level using an online software program and stratified for completion of the three-year master to specialize as a psychosomatic physiotherapist.

Allocation

- Patients will be treated by their physiotherapist and follow the intervention their physiotherapist was randomized to.

Blinding

- Patients cannot be blinded, but will only be informed about their own intervention and will neither be informed about the presence of two arms in the trial nor the intervention received in the other arm.
- Blinding of participating physiotherapists is not possible, due to the nature of the intervention.
- Blinding of coordinating researchers is not possible, as they need information about treatment allocation for adequate study coordination.
- Blinding of the analyses will be achieved by an independent statistician blinded for treatment allocation, who will perform the primary study analyses.

Sample size

- A clinically relevant between-group difference of at least 10 points on the ODI after 3-months follow-up is expected, which seems plausible based on recent pilot studies with VR from our research group and others. For this expected and clinically relevant difference of 10 and a standard deviation of 15, 60 patients are needed per group (a=0.05; power=90%; ICC for clusters 0.05; 15% drop-out). We expect to include 1 patient every 2 months per physiotherapist. A total of 20 participating physiotherapists will result in a total of 120 patients after 12 months.

Time schedule

- This study will start in the first quarter of 2023. Data collection will last until the first quarter of 2025.
- Approval from the medical-ethical committee (METC Oost-Nederland) was granted (case number: 2022-15794).
- The trial was registered with ClinicalTrials.gov (ID: NCT05701891).

Statistical principles

- All analyses in this plan are a priori analyses in that they have been defined in the protocol.
- All outcomes are analyzed for superiority of the experimental group in favor of the control group.
- All analyses described in the plan will take place after database locking, which will occur once all participants have finished their final measurement. An independent statistician that will be blinded for allocation will perform the main analyses.
- All statistical tests will be two-sided and the nominal p-value will be reported. All confidence intervals presented will be 95% and two-sided. The assumption of normal distribution will be checked by visual inspection of Q-Q plots. For skewed data, the interquartile range will be reported.
- Statistical significance is claimed if the null hypothesis is rejected at the significance level (alpha) of $p \leq 0.05$ (one-sided).
- Continuous variables will be summarized by means and SDs in case of a normal distribution and by median and interquartile range in case of a skewed distribution.
- Categorical variables will be summarized by frequencies and percentages.

Hypotheses

- This study is designed to assess the superiority of physiotherapy with integrated multimodal VR for patients with complex CLBP, compared to usual primary physiotherapy care on physical functioning at 3 months (primary end-point) and 12 months follow-up.
- The null hypothesis is that participants in the experimental group report a similar physical functioning score at 3 months and 12 months follow-up, as participants in the control group.
- The alternative hypothesis is that participants in the experimental group report a significantly higher score on physical functioning at 3 months and 12 months follow-up, as participants in the control group.

Analysis population

We will use the following definitions of analysis populations:

- The intention-to-treat population is defined as all participants provided informed consent and randomized to treatment.
- The per-protocol population is defined as all participants without minor and major protocol deviations.

We will decide which analysis populations each patient belong to in advance of database locking.

Protocol deviations

Major deviations

- For both treatment arms:
    - A total of <4 physiotherapy sessions or >30 physiotherapy sessions during intervention period (recommended: 8 – 25 sessions).
    - None of treatment modalities during the intervention period were exercise therapy or pain education.
    - Patient received invasive treatment (e.g. operation, injection or nerve block) for CLBP during intervention period.

- Specifically for experimental arm:
    - <300 minutes of VR use (50% of minimal dosage) during intervention period.

Minor deviations

- Specifically for experimental arm:
    - <480 minutes of VR use (80% of minimal dosage) during intervention period.

Trial population

- The following figures will be presented in a flow diagram, based on the CONSORT recommendations (figure 1):
    - Number of potentially eligible participants screened by the physiotherapist

- Number of included participants
- Reasons for non-inclusion
- Reasons for loss to follow-up and withdrawal
- Final inclusions in intention-to-treat analysis

Baseline patient and physiotherapist characteristics

- Participating patients will be described using the following baseline characteristics: age, sex, BMI, tobacco use, duration of complaints, comorbidities, occupation, education level, diagnostic and therapeutic procedures in past 6 months, medication use and experience with VR for treatment and entertainment, as shown in table 2. Moreover, participants will be described using the following clinical outcome measures: physical functioning, pain intensity, pain related fears, pain self-efficacy, physical activity level, problems with activities and intervention expectations.
- Participating physiotherapists will be described using the following baseline characteristics: age, gender, number of years' experience as a physiotherapist and specialization (i.e. finished with a master's degree), as shown in table 3.

Process evaluation

- The following process parameters regarding the physiotherapy treatment will be monitored by the physiotherapists for both arms: number of sessions, duration of sessions, applied treatment modality per session and adverse events (if applicable).
- In the experimental arm, the following VR related parameters will be additionally monitored using an online dashboard: treatment modality, daily treatment duration and VAS pain score (before and after VR use).

Analysis

Primary analysis

- The primary analysis will be an intention-to-treat, longitudinal mixed-model analysis comparing the effectiveness of physiotherapy with integrated multimodal VR for patients with complex CLBP, compared to usual primary physiotherapy care on physical functioning at 3 months (primary end-point) and 12 months follow-up.
- All participants in this study will be analyzed using mixed-models with maximum likelihood estimation.
- The analysis will be adjusted for important prognostic characteristics that potentially confound the treatment effects (e.g. physical functioning, pain severity, pain-related fears, BMI, tobacco use) and the baseline value of the outcome measure, with addition of other patient and/or physiotherapist characteristics that substantially differ between the two arms at baseline.

Secondary analysis

- Clinical effectiveness on secondary outcome measures:
    - The secondary effectiveness analysis will be performed similarly as the primary effectiveness analysis: an intention-to-treat, mixed-model analysis, to evaluate the effectiveness of physiotherapy with integrated multimodal VR for patients with complex CLBP, compared to usual primary physiotherapy care on pain intensity, pain related fears, pain self-efficacy and problems with activities at 3 months (primary end-point) and 12 months follow-up.

Cost-effectiveness

- Health-related Quality of Life: At baseline, 3, 6, and 12 months after start of the intervention, the participants' health states were assessed using the EuroQol 5D Health Questionnaire 3-level version (EQ-5D-5L). Using the Dutch EQ-5D-5L tariff, these health states were converted into utility values (0=dead; 1=full health). Quality-adjusted life-years (QALYs) were calculated using the area under the curve approach.
- Costs: In line with Dutch guidelines, costs were assessed from a societal perspective, meaning that all costs were included irrespective of who paid or benefited.

- Data on other healthcare utilization, informal care, unpaid productivity, and absenteeism. For the cost-utility and -effectiveness analyses, all participants included in the study will be analyzed, with missing data handled by using Multivariate Imputation by Chained Equations (MICE) and the number of imputed datasets will be determined using the loss of efficiency approach. Imputation models will include all available cost and effect measure values as well as variables differing between groups at baseline, variables related to the "missingness" of data and variables related to the outcomes. Pooled estimates will be calculated using Rubin's rules.
- Costs and effect differences will be estimated using Seemingly Unrelated Regression analyses, in which their possible correlation can be accounted for. The 95% confidence intervals surrounding the cost differences will be estimated using Bias-Corrected and Accelerated (BCA) bootstrapping. Subsequently, Incremental Cost-Effectiveness Ratios (ICERs) will be calculated by dividing the differences in costs by the differences in QALYs. Uncertainty surrounding the cost-differences and ICERs will be estimated using bias correct and accelerated (BCA) bootstrapping techniques (5000 replications) and be graphically illustrated by plotting BCA-bootstrapped cost-effect pairs on cost-effectiveness planes. Also, cost-effectiveness acceptability curves will be constructed to provide an indication of the probability of physiotherapy with integrated multimodal VR therapy being cost-effective with usual care at different values of willingness to pay.

Responder analysis

- The proportion of participants with a minimal clinically important difference (MCID), responders, on each of the outcome variables between treatment arms, at 3 months and 12 months follow-up:
    - 8 points improvement on the ODI (Hung et al., 2018)
    - 15% and/or 1-point improvement on the NRS (Salaffi et al., 2004)

Availability of data and materials

- The datasets generated and analyzed during the current study will be available in the Dataverse repository.
- The research protocol is accessible at ClinicalTrials.gov (ID: NCT05701891).

Figure 1. *Flow of participants*

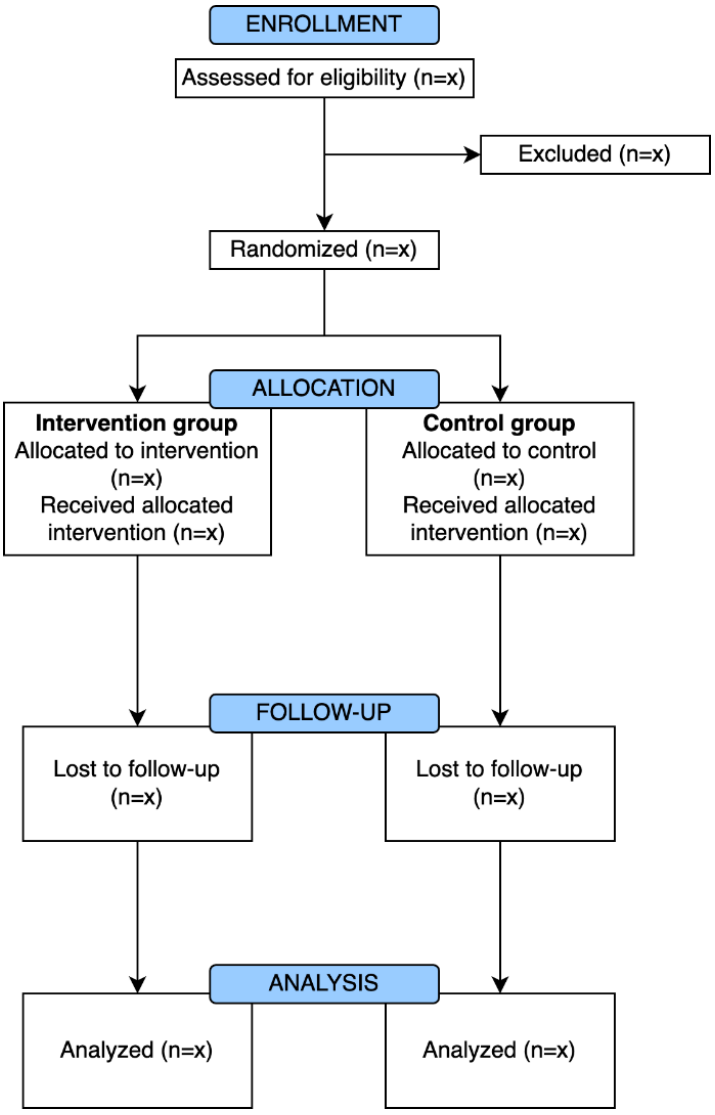

Table 1. *Overview of measurements*

	T0	T1	T3	T6	T12
Primary outcome measure					
Oswestry Disability Index (ODI)	X	X	X		X
Secondary outcome measure					
Numeric Rating Scale (NRS)	X	X	X		X
Fear Avoidance Beliefs Questionnaire (FABQ)	X	X	X		X
Pain Catastrophizing Scale (PCS)	X	X	X		X
Physical activity (self-reported)	X	X	X		X
Global perceived effect (GPE)		X	X		X
Patient-specific complaints questionnaire (PSK)	X		X		X
Pain self-efficacy (PSEQ)	X	X	X		X
Credibility and expectancy questionnaire (CEQ)	X	X			
Igroup presence questionnaire (IPQ)		X	X		
Economic parameters					
Quality-adjusted life years (QALY) (EQ-5D-5L)	X		X	X	X
Health-related and work-related costs	X		X	X	X
Patient characteristics	X				
Treatment parameters					
Other treatment than PT because of LBP, in past 12 weeks			X		
Duration of PT-treatment (number of weeks/sessions, reported by PT)			X		
Content of PT-treatment (usage of treatment modalities, reported by PT)			X		

Table 2. *Baseline characteristics*

	Experimental group (n =)	**Control group (n =)**
General characteristic		
Age (years), mean ± SD		
Sex (female (n)), %		
BMI, mean ± SD		
Smoker (yes), %		
Duration of symptoms (years), mean ± SD		
Work status Paid work (fulltime), % Pain work (parttime), % Unpaid work, % No work, but not retired, % Retired, % Student, %		
Use of pain medication (yes), %		
Comorbidities affecting daily life (count), %		
Diagnostic procedures for CLBP in past 6 months (yes), %		
Treatment for CLBP in past 6 months (yes), %		
Experience with VR for treatment (yes), %		
Experience with VR for entertainment (yes), %		

Table 3. *Physiotherapist characteristics*

	Experimental group (n =)	**Control group (n =)**
General characteristic		
Age (years), mean ± SD		
Sex (female), %		
Years' experience as physiotherapist (years), mean ± SD		
Specialization Manual, % Sport, % Psychosomatic, % Children, % Geriatric, % Orofacial, % Pelvic, % Oncology, %		

Table 4. *Primary and secondary outcome measures*

	Exp. (n=)	**Control (n=)**	**Est. diff. between groups**	
			Crude (95% CI, p-value)	**Adj. (95% CI, p-value)**
Primary clinical outcomes				
Physical function (ODI), mean ± SD				
Baseline 1 months follow-up 3 months follow-up 12 months follow-up				
Secondary clinical outcomes				
Pain intensity (NRS), mean ± SD				
Baseline 1 months follow-up 3 months follow-up 12 months follow-up				
Pain related fears (FABQ), mean ± SD				
Baseline 1 months follow-up 3 months follow-up 12 months follow-up				
Pain related fears (PCS), mean ± SD				
Baseline 1 months follow-up 3 months follow-up 12 months follow-up				
Physical activity, mean ± SD				
Baseline 1 months follow-up 3 months follow-up 12 months follow-up				
Global perceived effect (at least 'much improved'), %				
3 months follow-up				

	Exp. (n=)	Control (n=)	Est. diff. between groups	
12 months follow-up				
Activity level (PSK)				
Baseline 3 months follow-up				
Pain self-efficacy (PSEQ), mean ± SD				
Baseline 1 months follow-up 3 months follow-up 12 months follow-up				
Treatment expectation (CEQ), mean ± SD				
Baseline 1 months follow-up				
Sense of presence (IPQ), mean ± SD				
1 months follow-up 3 months follow-up				

Table 5: Costs per arm and cost differences across arms

Costs during 12-month follow-up period*	Experimental group (n=), mean costs in € (SE)	Control group (n=), mean costs in € (SE)	Crude mean cost difference in € (SE)	Adjusted* mean cost difference in € (SE)
Intervention-related costs				
Primary health care costs (other than intervention)[a]				
Secondary health care costs[b]				
Medication costs[c]				
Presenteeism costs				
Absenteeism costs				
Unpaid productivity costs				
Informal care costs				
Total costs				

SE = standard error, CI = confidence interval.

*adjusted for treatment arm, baseline costs, QALY, work status, gender, age

a. primary health care, other than the (experimental or control) intervention (e.g., general practitioner, acupuncturist);
b. secondary health care (e.g., hospital, rehabilitation center);
c. (prescribed and over-the-counter) medication for low back pain.

Table 6. *Cost-effectiveness analysis*

Analysis	Sample size		Outcome	ΔC (95 % CI)	ΔE (95 % CI)	ICER	Distribution CE-plane (%)			
	EXP	CON		€	Points	€/point	NE[a]	SE[b]	SW[c]	NW[d]
Main analysis—imputed dataset			ODI (0-100)							
			NRS pain (0-10)							
			QALYs (range: 0–1)							
SA1—health care perspective			ODI (0-100)							
			NRS pain (0-10)							
			QALYs (range: 0–1)							
SA2—human capital approach			ODI (0-100)							
			NRS pain (0-10)							
			QALYs (range: 0–1)							
SA3—complete cases for cost outcomes only			ODI (0-100)							
			NRS pain (0-10)							

Analysis	Sample size		Outcome	ΔC (95 % CI)	ΔE (95 % CI)	ICER	Distribution CE-plane (%)			
	EXP	CON		€	Points	€/point	NE[a]	SE[b]	SW[c]	NW[d]
			QALYs (range: 0–1)							
SA4-a – per protocol cases only (excluding major protocol violators only)			ODI (0-100)							
			NRS pain (0-10)							
			QALYs (range: 0–1)							
SA4-b– per protocol cases only (excluding major and minor protocol violators)			ODI (0-100)							
			NRS pain (0-10)							
			QALYs (range: 0–1)							