Health Economic Analysis Plan (HEAP) for:

Cost-effectiveness of individual supported work placements compared to usual case management for unemployed people with persistent pain

(working title)

Project	The ReISE project
Trial registration	ISRCTN85437524
Document date	18.02.2026

Introduction

Scope

This document is a supplement to the ReISE protocol (ISRCTN Identifier: ISRCTN85437524) [1] and comprises a health economic analysis plan (HEAP) for the article *"Cost-effectiveness of individual supported work placements compared to usual case management for unemployed people with persistent pain (working title)"*. The current HEAP has been written after data collection has finished. However, the HEAP will be uploaded to the ISRCTN registry before we enter the study database for the subsequent analyses.

Administrative information

Version of HEAP

1.0

Funding

This study is part of the ReISE project [2], which is funded by the Norwegian Research Council, through its Collaborative Project to meet Societal and Industry-related Challenges scheme (grant number 326732/ABHO).

Contributors to HEAP

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Signatures

I hereby declare that I have reviewed and approved the HEAP for this study.

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Study aim

The aim of this study is to evaluate the one-year cost-effectiveness of individual supported work placements compared to usual case management for unemployed people with persistent pain, from a societal perspective.

Method

The method of this study has been reported previously in the study protocol [1, 2]. For the cost effectiveness part of the study, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Cost-Effectiveness Analysis Randomised Clinical Trial taskforce recommendations [3], as well as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement [4] will be used. A summary of the method is presented below.

Design and setting

This study contains an economic evaluation embedded in a cohort randomised controlled trial with one year of follow-up in a Norwegian setting; the ReISE project [1, 2].

Study population, recruitment, and randomisation

Eligible participants were people aged 18 to 64 years who had been unemployed for at least one month, had experienced pain for more than three months, and expressed a desire to return to work. Exclusion criteria included having a job to return to (e.g., being on sick leave) and insufficient Norwegian or English language skills to answer questionnaires or communicate.

Participants were individually recruited through social media, charities (including pain and rheumatological organisations), Finn.no (a Norwegian job advertisement platform), and community health centres. Potential participants were directed to an online site providing study information and a consent form, they could contact the study team for further details or alternatively request to receive the study information and consent form by post. All included participants signed an informed consent form prior to study enrolment and were informed that they could withdraw at any time.

Participants were randomised to either usual case management or individual supported work placements and usual case management. Randomisation with minimisation was automated. The first participant was randomly allocated with equal probability, after which each subsequent participant had a two-thirds probability of being allocated to the group that best minimised imbalance in gender and age, initially maintaining an overall 1:3 allocation ratio to the intervention [5-7]. This ratio was subsequently altered from 1:3 to 1:2 and finally 2:1, for pragmatic reasons related to the flow of people through the intervention. A detailed description of the randomisation process is provided elsewhere [8].

Intervention

A comprehensive description of the rationale, development and content of the intervention can be found elsewhere [2]. Briefly, all participants were offered usual case management from the Norwegian Labour and Welfare Administration (NAV) for unemployed people with persistent pain in Norway. In addition, participants allocated to individual supported work placements received support from a case manager who explored work goals and barriers, coordinated a tailored work placement through a recruitment partner, and facilitated an individualised work plan. These participants also attended a two-day work-familiarisation group session and received culturally adapted, evidence-based information materials, while the case manager provided ongoing support and liaison with healthcare and placement providers as needed.

Data collection, effect and cost measures

At baseline, all participants responded to an electronic questionnaire including demographic variables and a set of patient-reported outcome measures. Follow-up questionnaires including health state were sent at 3, 6 and 12 months after inclusion. Data on healthcare utilisation were collected from public registries including the Norwegian Patient Registry (NPR) and the Norwegian Control and Payment of Health Reimbursements Database (KUHR). Data on productivity loss were collected from public registries (NAV), containing dates and grading of absenteeism, work assessment allowance, and disability pension, as well as the related diagnostic code, and contracted workhours. Data on healthcare utilisation and productivity loss were collected in the period from baseline to one year retrospectively, and in the one-year follow-up period. All information is stored and will be analysed securely through the Service for sensitive data (TSD) at the University of Oslo, Norway.

Effect measure

The effect measure of this study will be health-related quality of life expressed by quality-adjusted life-years (QALYs). First, health state of the participants was measured by the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) [9]. Second, the Norwegian EQ-5D-5L tariff [10] will be used to convert health states into utility scores (range −0.453 to 1), anchored at 0 'death' and 1'perfect health', with negative values representing health states perceived to be worse than death. QALYs will be estimated for each participant as area under the curve using the trapezoidal method [11], capturing both the duration and quality of health over the follow-up period and summarising each participant's overall health state in a single measure. QALYs remain undiscounted due to follow-up being confined to one year [11].

Cost measures

This study adopts a societal perspective; thus, both costs related to healthcare utilisation and productivity loss will be included. Healthcare utilisation was collected from public registries (NPR, KUHR) and included: primary healthcare use (e.g. general practitioner (GP), physiotherapist, chiropractor, and emergency room consultations) and secondary/tertiary healthcare use (outpatient contacts, day surgery, ordinary admission with overnight stay, and other admissions without overnight stay). Productivity loss was collected from public registries (NAV) and included productivity loss related to absenteeism, work assessment allowance, and disability pension.

Intervention costs will be estimated based on resource use associated with case managers, the two-day work-familiarisation group session, and placement managers, and valued using invoiced hours. Costs associated with usual case management are expected to be similar across the two groups, thus will not be included.

Sample size

This study contains secondary analyses embedded in a cohort randomised controlled trial. Details on sample size calculation related to the primary aim are provided elsewhere [2].

Statistical analyses

General analysis considerations

All analyses described in this HEAP are considered a priori in that they have been defined in the protocol and this HEAP. All post hoc analyses will be identified as such in the article if relevant. All analyses will be carried out using Stata, or other appropriate software.

Description of study flow

The flow of participants through the study will be reported with a flow chart according to the CONSORT guidelines [12]. Reasons for dropout will be provided where known. Differences between responders and non-responders will be evaluated.

Missing data

Cost information will be obtained from public registries (NPR, KUHR, NAV), in which all individuals receiving any form of benefits are registered by their social security number. Consequently, these data are expected to be complete. Missing EQ-5D-5L values at baseline and at 3, 6, and 12 months will be addressed if missingness is considered non-negligible (i.e., > 5%). Multiple imputation by chained equations (MICE) [13] will be applied under an assumption of missing at random, with values imputed jointly across all time points. The number of imputations will be set approximately equal to the percentage of incomplete cases [13]. The imputation model will include group allocation, EQ-5D-5L at all time points, total costs due to healthcare utilisation and productivity loss during a period of one year prior to inclusion, total costs due to healthcare utilisation and productivity loss during the follow up period, and the following self-reported baseline variables: age, sex, education level, pain severity, pain duration and workability. QALYs will be calculated within each imputed dataset using the trapezoidal method, and estimates will be pooled across imputations according to Rubin's rules [13]

Participant characteristics

Baseline characteristics of included participants will be presented as shown in Table 1.

Healthcare utilisation, productivity loss and cost estimation

Type and frequency of healthcare utilisation will be calculated for the entire follow up period. Days of productivity loss will be estimated and adjusted for grading of productivity loss. Healthcare utilisation and productivity loss will be presented in Appendix Table A1.

Costs of healthcare utilisation per participant will be estimated based on reimbursement rates collected from NPR and KUHR. Non-healthcare costs related to the provision of healthcare (such as transportation) will not be estimated. Costs related to productivity loss per participant will be estimated using the human capital approach, by multiplying number of workdays with complete productivity loss by an estimated national average wage rate (NOK2,827, assuming 252 workdays per year) including taxes and societal costs, obtained from Statistics Norway [14]. All costs will be presented in euros (€) 2024 and estimated with mean and standard deviation (SD) values for each cost category and treatment group, aggregated over the one-year follow-up period as shown in Table 2. Costs will remain undiscounted due to follow-up being confined to one year [11]. Norwegian prices will be recalculated to euros using the average annual exchange rate for 2024 published by the Norwegian Bank of Norway (€1=NOK11.6).

Cost effectiveness analysis

Cost effectiveness will be evaluated from a one-year societal perspective using a cost-utility analysis. Health effects will be measured in QALYs. Total societal costs will be estimated per participant as the sum of healthcare utilisation costs and productivity loss costs over the one-year follow-up period.

The analysis will be conducted using both the incremental cost-effectiveness ratio (ICER) and the net monetary benefit (NMB) approach. The ICER will be calculated by dividing mean difference in total costs (individual supported work placements and usual case management - usual case management) by mean difference in health effects gained over the one-year period (individual supported work placements and usual case management - usual case management). An ICER below the relevant willingness-to-pay (WTP) threshold per QALY gained indicates that individual supported work placements is considered cost-effective compared with usual case management. In Norway, the WTP threshold depends on the severity of the illness, which is assessed by calculating the absolute QALY shortfall. The absolute shortfall measures the difference in expected QALYs over a patient's remaining lifetime due to their illness compared to the general population without the disease. The WTP threshold is 275,000 NOK per QALY for absolute shortfalls of 4 QALYs or less, and it increases with severity, up to 825,000 NOK for shortfalls of 20 QALYs or more [15].

The NMB will be calculated as: NMB = ΔE x WTP – ΔC [16]. Where ΔE denotes the differences in QALYs, and ΔC the differences in costs between groups. A positive NMB indicates that individual supported work placements is considered cost-effective compared with usual case management at the specified WTP threshold [16].

Incremental costs and QALYs will be estimated using regression-based adjustment within a seemingly unrelated regression (SUREG) framework, allowing for correlation between costs and health outcomes. Total costs and QALYs will each be modelled as functions of group allocation, baseline EQ-5D-5L utility, total costs due to healthcare utilisation and productivity loss during a period of one year prior to inclusion, and the following self-reported baseline variables: age, sex, education level, pain severity, pain duration and workability.

To illustrate uncertainty surrounding the ICER, bootstrapped (10,000 replicated datasets) cost and effect pairs will be plotted on a cost effectiveness plane (CE plane) and a cost effectiveness acceptability curve (CEAC). Bootstrap resampling will be conducted at the participant level, with both cost and QALY equations re-estimated within each replicate to generate paired incremental cost and QALY estimates. A CE plane is divided into four quadrants: the northwest (NWQ), the northeast (NEQ), the southwest (SWQ) and the southeast (SEQ), representing all combinations of possible outcomes. If most incremental cost-effectiveness pairs (ICERs) are in the NWQ, the intervention being tested is assumed to be more costly and less effective than the benchmark (usual case management). Whereas the NEQ indicates that the intervention is more costly and more effective than the benchmark, the SWQ that the intervention is less costly and less effective, and the SEQ that the intervention is less costly and more effective. The CEAC will be used to demonstrate the probability that the intervention is cost-effective in comparison to the benchmark for a range of different WTP values (from 275,000 to 825,000 NOK).

Adjusted mean cost (€) and effect (QALYs) differences between the two groups, including ICER and CE plane distribution will be presented as shown in Table 3. NMB estimates will be reported in the text. The CE plane and CEAC will be presented with figures. The probability that individual supported work placements is cost-effective compared with usual case management will be assessed by jointly interpreting the ICER estimate alongside the NMB result, the CE plane, and the CEAC.

Sensitivity analysis

To assess credibility of the total cost estimates included in the cost effectiveness analysis, the calculation will be repeated without outliers. Outliers will be defined as participants with total costs above the 98th and 99th percentile. To evaluate the influence of single variables on the ICER and the NMB, a multiple one-way sensitivity analysis will be conducted, in which relevant costs and QALYs are varied by ± 20% from the estimates used in the main analysis. If multiple imputation is applied to handle missing data, the cost effectiveness analyses will be performed on complete case data to test credibility of the imputation procedure. Baseline characteristics of participants with complete versus incomplete EQ-5D-5L data will be compared to assess the plausibility of the missing-at-random assumption.

Ethics approval

This study is part of the ReISE project [1, 2]. The ReISE project has been approved by the Norwegian Regional Committee for Medical Research Ethics (reference no. 402918, REK South East A, 16/05/2022) and approved by the Norwegian Social Science Data Service (reference no. 861249) in 2018. A data protection impact assessment has been conducted to safeguard privacy in collaboration with the Norwegian Agency for Shared Services in Education and Research (reference no. 693603) in 2022.

Table 1. Participants characteristics and clinical status at baseline

	All participants (n=)	Missing, n (%)	Intervention group (n=)	Control group (n=)
Female, n (%)				
Age in years				
Education level, n (%)				
Mother tongue Norwegian, n (%)				
Pain severity average last week (NRS, 0-10)				
Pain area last month, n (%)				
Upper limb				
Lower limb				
Neck				
Back				
Chest				
Abdominal				
Head				
Others				
Pain duration, n (%)				
3-12 months				
> 1-3 years				
> 3-10 years				
> 10 years				
Health related QOL (EQ-5D-5L, -0.453-1)				
Confidence in return to work (0-10)				
Work ability (0-10)				
Perceived return to work duration, n (%)				
< 4 months				
4-10 months				
> 10 months				
*Healthcare utilisation prior to inclusion**				
Primary care consultation last 3 months, n (%)				
General practitioner				
Physiotherapist				
Chiropractor				
Emergency room				
Secondary/tertiary care last 3 months, n (%)				
Outpatient contact				
Day surgery				
Ordinary admission with overnight stay				
Other admissions without overnight stay				
*Productivity loss prior to inclusion***				
Days of sick leave last 3 months				
Days of work assessment allowance last 3 months				
Days of disability benefits last 3 months				

EQ-5D-5L indicates EuroQol 5 dimensions; NRS, Numeric Rating Scale. *Collected from public registies; the Norwegian Patient Registry (NPR) and the Norwegian Control and Payment of Health Reimbursements Database (KUHR). **Collected from the NAV registry, measured as calendar days, and adjusted for grading of productivity loss.

Table 2. Costs (€) due to healthcare utilisation and productivity loss throughout one-year of follow-up for both groups

Cost categories	Intervention group	Control group
Primary care		
General practitioner		
Physiotherapist		
Chiropractor		
Emergency room		
Total		
Secondary care		
Outpatient contact		
Day surgery		
Ordinary admission with overnight stay		
Other admissions without overnight stay		
Total		
Productivity loss		
Sick leave		
Work assessment allowance		
Disability benefits		
Total		
Total costs		
Total costs healthcare utilisation		
Total cost productivity loss		

Values are mean (SD) of costs (€)

Table 3. Mean cost (€) and effect (QALYs) differences (95% CI) between the intervention and control group during the one-year follow-up, including ICER, and cost-effectiveness plane distribution

	Δ costs (95% CI)	Δ QALYs (95% CI)	ICER	Distribution CE-plane (%)[a]			
				NEQ	SEQ	SWQ	NWQ
Intervention group			-	-	-	-	-
Control group			-	-	-	-	-
Incremental							

CE-plane indicates cost-effectiveness plane; ICER, incremental cost-effectiveness ratio; NEQ, Northeast-Quadrant; NWQ, Northwest-Quadrant, SEQ, Southeast-Quadrant; SWQ, Southwest-Quadrant; QALY, quality-adjusted life year. QALYs are based on EuroQol's health-related quality of life measure (EQ-5D-5L) with scores from −0.453 to 1. Higher scores indicating better quality of life. ICER = (cost intervention group - cost control group) / (QALY intervention group - QALY control group). Estimates are pooled based on multiple imputation and adjusted for baseline EQ-5D-5L utility, prior healthcare utilisation and productivity loss costs, age, sex, education level, pain severity, pain duration and workability. [a]Estimates based on bootstrapping (10 000 replicated datasets).

Table A1. Healthcare utilisation and productivity loss throughout one-year of follow-up

	All participants (n=)	Missing, n (%)	Intervention group (n=)	Control group (n=)
Primary care				
Participants with primary care consultation, n (%)				
General practitioner				
Physiotherapist				
Chiropractor				
Emergency room				
No primary care consultation				
Numbers of consultations, median (IQR)*				
General practitioner				
Physiotherapist				
Chiropractor				
Emergency room				
Secondary/tertiary care				
Participants with secondary/tertiary care consultation, n (%)				
Outpatient contact				
Day surgery				
Ordinary admission with overnight stay				
Other admissions without overnight stay				
No secondary/tertiary care consultation				
Numbers of consultations, median (IQR)*				
Outpatient contact				
Day surgery				
Ordinary admission with overnight stay				
Other admissions without overnight stay				
Duration of ordinary admission with overnight stay in days, median (IQR)**				
Productivity loss				
Participants with productivity loss, n (%)				
Sick leave				
Work assessment allowance				
Disability benefits				
Duration of productivity loss in days, median (IQR)***				
Sick leave				
Work assessment allowance				
Disability benefits				

*Calculated on basis of participants who have reported primary/secondary/tertiary care consultations. **Calculated on basis of participants who have reported ordinary admission with overnight stay. ***Calculated on basis of participants who have reported productivity loss, converted into a 5-day workweek, and adjusted for grading of productivity loss.

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