

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email editorial.bmjopen@bmj.com

BMJ Open

Return-to-work intervention for sick-listed employees with common mental disorders versus usual psychiatric care: cost-benefit analysis alongside a cluster randomised trial

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2017-016348 |
| Article Type: | Research |
| Date Submitted by the Author: | 08-Feb-2017 |
| Complete List of Authors: | Lokman, Suzanne; Trimbos-institute, Public Mental Health Volker, Danielle; Trimbos-institute Zijlstra-Vlasveld, Moniek; Trimbos-institute, Public Mental Health Brouwers, Evelien; Tilburg University Tilburg School of Social and Behavioral Sciences Boon, Brigitte; Trimbos-institute Beekman, Aartjan; EMGO Institute for Health and Care Research; VU University Medical Center Amsterdam, Department of Psychiatry Smit, Filip; Trimbos-institute, Public Mental Health; VU University Medical Centre, Department of Epidemiology and Biostatistics Van der Feltz-Cornelis, Christina; 7GGZ GGZ Breburg, TopClinical Centre for Body, Mind and Health; Tilburg University Tilburg School of Social and Behavioral Sciences, Tranzo |
| Primary Subject Heading: | Occupational and environmental medicine |
| Secondary Subject Heading: | Health economics |
| Keywords: | mental disorder, absenteeism, return to work, eHealth, cost-benefit |
| | |

SCHOLARONE™
Manuscripts

TITLE PAGE**Return-to-work intervention for sick-listed employees with common mental disorders versus usual psychiatric care: cost-benefit analysis alongside a cluster randomised trial**

Suzanne Lokman, Danielle Volker, Moniek C Zijlstra-Vlasveld, Evelien PM Brouwers, Brigitte Boon, Aartjan TF Beekman, Filip Smit, Christina M van der Feltz-Cornelis

Trimbos-institute, Netherlands institute of mental health and addiction, Department of Public Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands, Maastricht University, Department of Health Services Research, CAPHRI School of Public Health and Primary Care, PO Box 616, 6200 MD Maastricht, The Netherlands Suzanne Lokman
economist

Trimbos-institute (Netherlands institute of mental health and addiction), Department of Public Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands, Tilburg University, School of Social and Behavioral Sciences, Department Tranzo, PO Box 90153, 5000 LE Tilburg, The Netherlands Daniëlle Volker
psychologist

Trimbos-institute, Netherlands institute of mental health and addiction, Department of Public Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands Moniek C Zijlstra-Vlasveld
psychologist
Tilburg University, School of Social and Behavioral Sciences, Department Tranzo, PO Box 90153, 5000 LE Tilburg, The Netherlands Evelien P.M. Brouwers
psychologist

Trimbos-institute, Netherlands institute of mental health and addiction, Department of Public Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands Brigitte Boon
head of Department of public mental health
Department of Psychiatry and the EMGO+ Institute for Health and Care Research, VU University Medical Center, AJ Ernststraat 1187,1081 HL Amsterdam, The Netherlands Aartjan TF Beekman
professor of psychiatry

Trimbos-institute, Netherlands institute of mental health and addiction, Department of Public Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands, Department of Clinical, Neuro and Developmental Psychology, and Department of Epidemiology and Biostatistics EMGO+ Institute for Health and Care Research, VU University Medical Center, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands Filip Smit
professor of public mental health

1
2
3 Tilburg University, School of Social and Behavioral Sciences, Department Tranzo, PO Box
4 90153, 5000 LE Tilburg, The Netherlands, Clinical Centre of excellence for Body Mind and
5 Health, GGz Breburg, PO Box 90153, 5000 LE Tilburg, The Netherlands Christina M. van der
6 Feltz-Cornelis
7
8 professor of social psychiatry
9

10
11 Correspondence to: slokman@trimbos.nl
12

13
14 Key words: mental disorders, absenteeism, return to work, eHealth, cost-benefit
15 Word count: 4874; Number of figures: 1; Number of tables: 3; Number of references: 42
16 Number of supplementary files for online only publication: 0
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Return-to-work intervention for sick-listed employees with common mental**
4 **disorders versus usual care: cost-benefit analysis alongside a cluster randomised**
5 **trial**
6

7
8 **ABSTRACT**
9

10 **OBJECTIVE:** To evaluate the economic costs and benefits of a guided eHealth intervention
11 (ECO) encouraging sick-listed employees to make an early return to work.
12
13

14
15 **DESIGN:** Data of a 2-armed cluster randomised trial were analysed to conduct a cost-benefit
16 analysis from different perspectives. Online self-reported data were collected from the
17 employees at baseline and after 3, 6, 9 and 12 months.
18
19

20
21 **SETTINGS:** 62 occupational physicians (OPs) in the Netherlands. OPs working in the same
22 region were clustered and randomised into an experimental and a control group.
23
24

25 **PARTICIPANTS:** Employees working at small-sized and medium-sized companies (≥ 18 years)
26 and sick-listed between 4 and 26 weeks with common mental disorders visiting their OP.
27
28

29
30 **INTERVENTIONS:** Employees in the intervention group (N=131) received an eHealth module
31 aimed at changing cognitions regarding return to work, while the OPs were supported by a
32 decision aid for treatment and referral options. Employees in the control condition (N=89)
33 received usual sickness guidance.
34
35

36
37 **OUTCOMES MEASURES:** The number of days absent, resource use, and quality adjusted life
38 years (QALYs) gained.
39
40

41
42 **RESULTS:** From the employer's perspective, the incremental net-benefits were €3,187 per
43 employee over a single year, representing a return of investment of €11 per invested Euro,
44 with a break-even point at six months. The economic case was also favourable from the
45 employee's perspective, in part because of QALY health gains. However, the intervention was
46 costing €213 per employee from a health service financier's perspective. The incremental net-
47 benefits from a social perspective were €3,537. This amount dropped to €2,928 in the
48 sensitivity analysis trimming the 5% highest costs.
49
50
51
52

53 **CONCLUSIONS:** The data suggest that the ECO intervention offers good value for money for
54 virtually all stakeholders involved, because initial investments were more than recouped within
55 a single year, but the wide 95% confidence intervals require careful interpretation.
56
57
58
59
60

1
2
3 **TRIAL REGISTRATION:** Netherlands Trial Register NTR2108

4
5 Key words: mental disorders, absenteeism, return to work, eHealth, cost-benefit

6 Word count: 4874; Number of figures: 1; Number of tables: 3; Number of references: 42

7
8 Number of supplementary files for online only publication: 0
9

10 11 12 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 13
14
15 • The analysis was based on the results of a randomised controlled trial, comparing the
- 16 intervention to usual care.
- 17
18 • This study adds to the only few available studies that present a trial-based investment
- 19 appraisal of the economic costs and benefits of a return to work intervention for sick-
- 20 listed employees
- 21
22 • The trial was only powered to test a difference in sickness absence duration and not for
- 23 testing economic hypotheses.
- 24
25 • The follow-up time is limited to 12 months.
26
27

28 29 **INTRODUCTION**

30
31 Long-term sickness absence has a significant economic impact, largely due to the substantial
32 productivity losses.[1, 2] Mental disorders are a leading cause of sickness absence,[3-6] which
33 is not without economic ramifications.[7] Common mental disorders, specifically depression
34 and anxiety, are the most prevalent in the workforce.[8]
35
36

37
38 For the treatment of common mental disorders a range of psychological and pharmaceutical
39 interventions have been shown to be effective and cost-effective.[9, 10] However,
40 symptomatic recovery does not automatically reduce sickness absence.[10-12] To improve
41 occupational outcomes it is also important to pay attention to return to work during treatment.
42
43
44

45
46 In the Netherlands, occupational physicians (OPs) provide sickness guidance.[13] A guideline
47 has been developed to suggest directions to OPs to better assist employees with mental health
48 problems in the return to work process. According to this guideline, the OPs need to closely
49 monitor both the mental health problems and the level of functioning. When recovery is slow
50 or hampered, they can consult or refer to a psychiatrist, a psychologist or a social worker.[14]
51 A study of Rebergen and colleagues suggested that better adherence to the guideline is
52 associated with earlier return to work.[15] However, in practice, adherence appears to be far
53 from optimal,[16, 17] and there is often a lack of cooperation between the OPs and treatment
54 providers in the mental health sector. Several attempts have been made to bridge this gap.
55
56
57
58
59
60

1
2
3 One study about the effect of psychiatric consultation for OPs assisting sick-listed employees
4 did provide results in terms of earlier return to work.[18] However, this study was small.
5
6 Another study evaluating active treatment by an OP within a collaborative care arrangement
7 did improve depressive symptoms, but failed to speed up return to work.[19] It appeared that
8 OPs need support in helping sick-listed employees change their attitude towards resuming
9 work and should monitor symptom improvement and work performance in a more systematic
10 manner.
11
12

13
14 To overcome these problems and to better manage the return to work of sick-listed employees
15 with common mental disorders, the "E-health module embedded in Collaborative Occupational
16 health care" (ECO) intervention was developed. The ECO intervention was designed to promote
17 return to work by improving work functioning in employees, providing a decision aid for the OP
18 who gives guidance to the employee, and by including the opportunity for psychiatric
19 consultation to the OP.[20]
20
21
22
23

24
25 The results of a recent trial showed that ECO led to an earlier first return to work than usual
26 care (mean duration of 77 days in the ECO group versus 50 days in the CAU group) and higher
27 remission rates of common mental disorder after 9 months in a group of sick-listed employees
28 with common mental disorders.[21]
29
30
31

32 Taking the economic perspective, we expect that the ECO intervention is cost-effective as seen
33 from the employer's viewpoint, because ECO is a low cost self-help intervention with a limited
34 amount of support from the OP and appears to be effective in reducing absenteeism. There is
35 less certainty how cost-effective the intervention would be as seen from the perspective of the
36 sick-listed employees and the health care financier (i.e. health care insurance company in the
37 Dutch context). Therefore, this study conducts a costs-benefit analysis of the ECO intervention
38 from all three stakeholders' viewpoints, and combines these in an overarching societal
39 perspective. These analyses are important because very few trial-based economic evaluations
40 have been conducted with regard to return-to-work interventions for sick-listed employees
41 with common mental disorders.[12, 22]
42
43
44
45
46
47

48 **METHOD**

49 **Study design**

50
51 The ECO study was designed as a 2-armed cluster randomised controlled trial, with
52 randomisation at the level of the OP and sick-listed employees either randomised to usual care
53 or usual care plus the ECO intervention. The Netherlands Organization for Health Research and
54 Development funded the study (grant number 171002403 ZonMw Doelmatigheid) together
55
56
57
58
59
60

1
2
3 with Achmea, a Dutch insurance company. The Medical Ethics Committee of the University
4 Medical Center Utrecht approved the study protocol in 2011, and the trial was registered at the
5 Netherlands Trial Register (NTR) under number 2108. The design of the study is described in
6 detail elsewhere.[20, 21] Here, we provide a brief summary of the main characteristics and
7 focus on the economic aspects.
8
9

10 11 **Randomisation**

12 To prevent contamination cluster randomisation took place at the level of the OPs working in
13 the same region across a total of twelve regions. An independent statistician randomised six
14 regions to the ECO condition and the remainder to the control condition using computer-
15 generated randomisation. Since the OPs had to offer the intervention, they could not be
16 blinded for randomisation. The researchers and participants were informed about the allocation
17 after the randomisation procedure.
18
19
20
21

22 23 **Participants**

24 Participants were recruited from July 2011 to January 2013 from all-cause sick-listed
25 employees working at small-sized and medium-sized companies in the Netherlands who visited
26 an OP. To be eligible for inclusion the employees had to be at least 18 years of age and on
27 sickness absence between 4 and 26 weeks. In addition, they needed to have a score ≥ 10 on
28 either the depression or the somatization scale of the Patient Health Questionnaire (PHQ-
29 9),[23, 24] or the Generalized Anxiety Disorder questionnaire (GAD-7).[25] Exclusion criteria
30 were (1) poor command of the Dutch language, (2) pregnancy, (3) not having access to the
31 Internet, (4) being involved in a legal action against the employer.
32
33
34
35
36
37

38 39 **Procedure**

40 Initially an independent statistician randomised 12 regions to either CAU (6 regions with 30
41 OPs) or ECO (6 regions with 32 OPs) by using a computer algorithm. Within the cluster of CAU
42 regions 5,875 sick-listed employees were screened for eligibility resulting in 326 screen-
43 positives. In the cluster of ECO regions, 537 screen-positives were obtained from 8740 sick-
44 listed employees. Next, 89 and 131 consenting participants were randomised to CAU and ECO,
45 respectively. The unequal distribution of participants over the conditions was due to cluster
46 randomisation. Participants received measurements at baseline and at 3, 6, 9 and 12 months,
47 which amounted to dropout in both conditions (see figure 1).
48
49
50
51
52

53 Figure 1. Flowchart of the participants
54
55
56
57
58
59
60

Intervention

ECO consists of 2 components: (1) the eHealth module Return@Work for the employee and (2) an email-based decision-aid to support the OP. Return@Work is aimed at improving the self-efficacy of employees and promoting the employee's intention to return to work. Recent studies have shown that these factors are predictors of actual work resumption.[26-28] The decision-aid provides the OPs with advice regarding treatment and referral options based on the employee's outcome monitoring in Return@Work.

The eHealth module starts with an assessment questionnaire. Depending on the results of the questionnaire regarding symptoms and cognitions about return to work of the individual employee, Return@Work presented specific modules and sessions. As a consequence, the amount of modules and sessions offered to the employees differed. In total, Return@Work included 5 modules composed of 16 sessions, covering: 1) psycho-education, 2) cognitions regarding return to work while having symptoms (based on principles of cognitive behavioural therapy), 3) problem solving skills, 4) pain and fatigue management and reactivation, and 5) relapse prevention. The employees went through the modules independently, but had the possibility to discuss Return@Work modules and assignments with the OP. The OPs were requested to inquire about the employee's progress in the eHealth module and to provide support if necessary during their regular face-to-face contacts with the employee. Periodic visits between the employee and the OP are part of the guidelines of the Dutch Board for Occupational Medicine (NVAB),[14] which all OPs were required to adhere.

Besides the modules, Return@Work also contained a monitor of functioning and symptoms on a regular basis. This monitor was used for the second component of ECO, a decision aid to support OPs in the sickness guidance of employees. Based on the outcomes of the monitor in Return@Work the OPs received automated email messages with advice for next steps in collaborative care. In addition, the decision aid gave OPs the option to consult a psychiatrist in case insufficient progress was made. The OPs in the experimental condition received a 4-hour training about ECO.

In the control condition the employees received usual sickness guidance. The guidelines of the NVAB were used as a protocol.[14] As there is a lack of adherence to the guidelines,[16,17] actual care was assessed with a questionnaire by all of the participating employees.

Outcome measures

Participants filled in the Medical Technology Assessment Cost Questionnaire for Psychiatry (TiC-P),[29] which amongst health care use also measures absenteeism from work, which is the main outcome variable of this study. The TiC-P is based on self-report and to crosscheck

1
2
3 the number of work days lost to absenteeism we compared the self-reports with administrative
4 data (see Sensitivity Analysis below). Total follow-up time was 12 months with measurements
5 at baseline and after 3, 6, 9 and 12 months. Finally, health gains in terms of quality adjusted
6 life years (QALYs) were assessed using the EuroQoL-5D-3L,[30] with the Dutch tariff.[31]
7
8

9 10 **Resource use and costing**

11 Cost data were collected using the TiC-P, including (1) direct medical costs, including the costs
12 of medication, (2) direct non-medical costs (patients' out-of-pocket costs for trips to health
13 services), (3) costs stemming from productivity losses owing to absenteeism and
14 presenteeism, and (4) costs that occurred in the domestic realm (help for housekeeping from
15 family, friends or hired people). Standard costs, expressed in euro (€), were indexed for the
16 reference year 2011 using the consumer price index from Statistics Netherlands. Costs were
17 not discounted because the follow-up period did not exceed one year.
18
19
20
21
22

23 **Computation of costs**

24 The set costs of the ECO intervention are €300 per user, which is its current (post trial) rate.
25 Direct medical costs are limited to mental health service use. The medical costs were
26 computed by multiplying the number of health service units (sessions, visits, hospital days)
27 with their standard full economic cost price.[32] Only medication costs for mental problems
28 were included in the economic analysis. For every type of drug (e.g. antidepressants,
29 benzodiazepines, antipsychotics, problems sleeping) an average cost price was calculated
30 based on the cost prices per standard daily dose of three drugs most often prescribed to the
31 participants as reported in the Pharmaceutical Compass,[33] while taking into account the GP's
32 prescription costs, the pharmacist's dispensing costs and the pharmacist's claw back as per the
33 guideline for cost computations in health care.[32]
34
35
36
37
38
39
40

41 The direct non-medical costs consisted of the travel costs that participants had to make to visit
42 OPs and health services. These costs were calculated as the average distance to the specific
43 health service provider multiplied by the costs per km (€0.21) plus parking costs (€3.11) per
44 hour. To the direct non-medical costs we added the costs in the domestic realm, computed by
45 multiplying €12.96 by the number of hours that others (family and friends) took over cleaning
46 and running domestic errands.
47
48
49

50
51 In the Netherlands QALY health gains are valued at €50,000 per QALY with a range between
52 €20,000 and €80,000.[34] We used the conservative threshold of €20,000 for our analysis.
53
54

55
56 Productivity losses comprised the costs of lost workdays due to absenteeism and the costs of
57 inefficiency while at work (presenteeism). We used the human capital method to value the
58
59
60

1
2
3 productivity costs.[35] In the case of absenteeism, this method multiplies the number of days
4 absent by the gender and age-specific average gross wages per employee, as per the Dutch
5 guideline for health economic evaluation.[32] To assess the costs of presenteeism we used the
6 number of days actually worked when ill multiplied by a self-reported inefficiency score. This
7 score ranged from 0 (as effective as in good health) to 1 (totally ineffective). Again, the
8 gender and age-specific average gross wages were used to compute the costs of presenteeism.
9
10
11

12 13 **Analyses**

14 Following recommendations from the CONSORT and CHEERS statements,[36-38] analyses
15 were conducted in agreement with the intention to treat principle. Therefore all participants as
16 randomised were retained in the analysis and missing observations due to dropout were
17 imputed. For imputation we used both the estimation-maximisation (EM) algorithm as
18 implemented in SPSS for the main analysis, and regression imputation (RI) as implemented in
19 Stata for the sensitivity analysis (see below). In both imputation strategies we used predictors
20 of outcomes (costs and QALYs) and predictors of dropout (age, gender, partner status, country
21 of birth, number of work loss days). Predictors of the outcomes were included to increase
22 precision in the imputed values, predictors of dropout were incorporated to tackle selection-
23 bias, if any, and to meet the missing at random (MAR) assumption underlying most imputation
24 techniques.
25
26
27
28
29
30
31

32 The economic evaluation was conducted as an incremental cost-benefit analysis, because the
33 primary outcome (duration of sick leave) could directly be expressed in terms of monetary
34 benefits. The costs and benefits were calculated at baseline, 3, 6, 9 and 12 months in the ECO
35 and CAU conditions. The costs in the intermediate months were linearly interpolated. This
36 allowed mapping the monthly cash flows of costs and benefits over the full 12-month period.
37 The cash flows were computed from four perspectives: (1) the employer's perspective
38 focussing on the net-benefits from greater productivity via lesser absenteeism and lesser
39 presenteeism; (2) the health care perspective focussing on the direct medical costs due to
40 health service use, including the costs of medication, (3) the employee's perspective focussing
41 on QALY health gains, fewer out-of-pockets costs and fewer costs in the domestic realm.
42 Finally, we included a societal perspective (4), including all costs and benefits, regardless of
43 who incurs costs or receives benefits.
44
45
46
47
48
49
50

51 The monthly cash flows were used to compute the cumulative costs and cumulative monetary
52 benefits over the full twelve months. Incremental costs, incremental benefits and incremental
53 net-benefits were obtained by comparing ECO intervention with CAU. These are the main
54 outcomes of the economic analysis alongside metrics such as the break-even point and the
55 return on investment (ROI).
56
57
58
59
60

1
2
3
4 For statistical analysis we relied on non-parametric bootstrapping (2,500 replications) since
5 costs are non-normally distributed. Statistics such as mean costs, 95% confidence intervals,
6 standard errors and p-values are all based on non-parametric bootstrapping to increase the
7 robustness of our findings. The data were analysed in SPSS (version 22) and Stata (version
8 13.1).
9
10
11

12 13 **Sensitivity analysis**

14 The main analysis (using the overarching societal perspective and based on EM imputation)
15 was repeated three times in a series of sensitivity analyses. Firstly, the analysis was conducted
16 again, but now based on regression imputation (RI) to assess the robustness of the findings
17 under a different imputation technique. Secondly, we crosschecked the self-reported
18 absenteeism against administrative data derived from the registers of the occupational health
19 service or the employer, because the main analysis was based on self-reports and some recall
20 bias (underreporting) could have occurred. Finally, we recalculated the incremental net-
21 benefits after trimming the highest 5% of total cumulative costs per employee, because the
22 participants with the extremely high costs were only a small minority but may have exercised
23 a disproportional influence on the cost estimates and pushed outcomes to a more favourable
24 outcomes for the ECO intervention. By excluding these participants, primarily from the CAU
25 condition, the net-benefits were re-estimated but now under conservative assumptions.
26
27
28
29
30
31
32
33

34 **RESULTS**

35 36 **Sample characteristics and baseline costs**

37 Baseline characteristics of the sample (including baseline costs) are presented in table 1. The
38 mean age of the 220 participants was 44 years and 59% was women. No important differences
39 were observed at baseline in demographic characteristics and quality of life, but baseline costs
40 were somewhat higher in the ECO condition, suggesting that the ECO group had a slightly
41 disadvantageous start. We will return to this issue in the Discussion. As described by Volker
42 and colleagues,[21] job characteristics and sickness absence duration at baseline were also
43 comparable between the intervention condition and control condition, indicating that the
44 randomisation was generally well balanced.
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1. Baseline characteristics in the care as usual (CAU) and the ECO intervention group

| | CAU (n=89) | ECO (n=131) |
|--|--------------|--------------|
| Age, mean (SD) | 45.5 (10.7) | 43.3 (9.5) |
| Female, N (%) | 53 (59.6) | 77 (58.8) |
| Married/living together, N (%) | 62 (69.7) | 91 (69.5) |
| Educational level, N (%) | | |
| Low | 32 (36.0) | 48 (36.6) |
| Average | 31 (34.8) | 47 (35.9) |
| High | 26 (29.2) | 36 (27.5) |
| Country of birth: The Netherlands, N (%) | 83 (93.3) | 123 (93.9) |
| Direct medical costs, mean (SD) | 645 (58) | 602 (49) |
| Direct non-medical costs, mean (SD) | 35 (2) | 33 (2) |
| Absenteeism, mean (SD) | 2850 (146) | 3078 (125) |
| Presenteeism, mean (SD) | 34 (16) | 20 (14) |
| Costs in the domestic realm, mean (SD) | 143 (26) | 133 (20) |
| Medication, mean (SD) | 8 (2) | 12 (3) |
| Total costs, mean (SD) | 3716 (154) | 3879 (141) |
| Quality of life, mean (SD) | 0.57 (0.027) | 0.54 (0.024) |

Loss to follow-up

The measurements at 3, 6, 9 and 12 months were completed by 155 (70.5%), 157 (71.4%), 134 (60.9%) and 128 (58.2%) of the participants. The dropout rate over the 12-month trial period was higher in the ECO condition (45.0%) than the control condition (37.1%), but this difference was statistically insignificant ($\chi^2=1.38$; $df=1$; $p=0.240$). As indicated, we looked for variables that predict dropout and included these as predictors in the EM and IR imputations. This was done to counter selection-bias (if any) and to better meet the MAR assumption underpinning the imputation strategies.

Costs and QALYs at 3, 6, 9 and 12 months

The next step of the cost benefit analyses was to ascertain costs and quality of life at the follow-up measurements (Table 2). Cost differences were highest for absenteeism. At 12 months all the cost differences were statistically significant and in favour of the ECO condition. The total costs difference at the 12 month follow-up amounted to €919 (SE=205; $z=4.48$; $p<0.001$), mainly due to reduced absenteeism.

Table 2. Average monthly costs in the care as usual (CAU) and the ECO intervention group at 3, 6, 9 and months (in 2011 Euro)^{1, 2}

| | 3 months | 6 months | 9 months | 12 months |
|----------------------------------|----------|----------|----------|-----------|
| Direct medical costs | | | | |
| CAU | 474 | 298 | 383 | 296 |
| ECO | 460 | 473 | 311 | 144 |
| Cost difference | 14 | -175 | 71 | 153 |
| Direct non-medical costs | | | | |
| CAU | 135 | 74 | 102 | 98 |
| ECO | 104 | 89 | 67 | 45 |
| Cost difference | 31 | -15 | 35 | 53 |
| Productivity losses | | | | |
| Absenteeism | | | | |
| CAU | 2120 | 1699 | 1276 | 1118 |
| ECO | 1887 | 1264 | 725 | 572 |
| Cost difference | 233 | 435 | 551 | 546 |
| Presenteeism | | | | |
| CAU | 166 | 233 | 269 | 493 |
| ECO | 357 | 408 | 322 | 325 |
| Cost difference | -191 | -175 | -53 | 168 |
| Total costs | | | | |
| CAU | 2895 | 2305 | 2029 | 2005 |
| ECO | 2808 | 2234 | 1425 | 1085 |
| Cost difference | 87 | 70 | 605 | 919 |
| Quality of life (utility) | | | | |
| CAU | 0.65 | 0.68 | 0.68 | 0.73 |
| ECO | 0.65 | 0.72 | 0.76 | 0.77 |
| Difference in utilities | 0 | 0.04 | 0.08 | 0.04 |

1 Between-group differences in italics are statistically significant at $p < 0.05$.

2 Numbers may not add due to rounding

Cost-benefit analysis: employer's perspective

For the employer's perspective only the intervention costs and costs stemming from absenteeism and presenteeism were included, thus assuming that the employer would be interested to know the pay out of this investment when paying for the intervention. Cumulated over the 12-months period the incremental benefits were €3,487 in favour of the ECO condition (Bootstrapped 95% CI= -418~7,390; SE=1,992; $z=1.75$; $p=0.080$), which was mainly due to a larger reduction in absenteeism over 12 months compared to care as usual (bootstrapped M=4,291; 95% CI= 290~8,292; SE=2,041; $z=2.10$; $p=0.036$). Next, we calculated incremental net-benefits, by subtracting the intervention costs (€300) from the incremental benefits. As shown in table 3 the incremental net-benefits over twelve months were €3,187 per employee in favour of the ECO condition, but there is significant uncertainty

in the estimate (Bootstrapped 95% CI=-656~7,029; SE=1,961; z=1.63; p=0.104). We return to this issue in the Discussion. The break-even point for the employer, the moment in time where the investment of €300 is recouped, is around six months. The return of investment (ROI) is $3,187 / 300 = 10.62$, indicating that for every euro invested the pay-out is €10.62.

Table 3. Monthly per patient costs in the care as usual (CAU) and the ECO intervention group from an employer's perspective (in 2011 Euro)

| Month | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Cumulative |
|--------------------------|------|------|------|------|------|------|------|------|------|------|------|------|------------|
| CAU | | | | | | | | | | | | | |
| Absenteeism | 2850 | 2485 | 2120 | 1910 | 1910 | 1699 | 1487 | 1487 | 1276 | 1197 | 1197 | 1118 | 20736 |
| Presenteeism | 34 | 100 | 166 | 199 | 199 | 233 | 251 | 251 | 269 | 380 | 380 | 493 | 2955 |
| Total costs | 2884 | 2585 | 2286 | 2109 | 2109 | 1932 | 1738 | 1738 | 1545 | 1577 | 1577 | 1611 | 23691 |
| ECO | | | | | | | | | | | | | |
| Absenteeism | 3078 | 2483 | 1887 | 1576 | 1576 | 1264 | 994 | 994 | 725 | 648 | 648 | 572 | 16445 |
| Presenteeism | 20 | 188 | 357 | 382 | 382 | 408 | 365 | 365 | 322 | 323 | 323 | 325 | 3760 |
| Total costs | 3098 | 2671 | 2244 | 1958 | 1958 | 1672 | 1359 | 1359 | 1047 | 971 | 971 | 897 | 20205 |
| Incremental benefits | -214 | -86 | 42 | 151 | 151 | 260 | 379 | 379 | 498 | 606 | 606 | 714 | 3486 |
| Intervention costs | -300 | | | | | | | | | | | | |
| Incremental net-benefits | -514 | -600 | -558 | -407 | -256 | 4 | 383 | 762 | 1260 | 1866 | 2472 | 3186 | |
| Return on investment | 10,6 | | | | | | | | | | | | |

Cost-benefit analysis: health care payer's perspective

For the perspective of the health care financier (in the Netherlands: health care insurers) we looked at the direct medical costs including the costs for medication. We computed the monthly cash flows and compared these between the ECO and CAU conditions as before. The cumulative costs over twelve months were more or less the same for each condition with a small difference of €87 in favour of the ECO condition. Assuming that the health insurer would pay for the intervention, the intervention costs of €300 have to be subtracted from these benefits in order to obtain the net-benefits. This generated a negative value of €213, implying that the ECO intervention is not cost saving from a health care insurer's perspective (bootstrapped 95% CI=-1,384~959; SE=598; z=-0.36; p=0.722).

Cost-benefit analysis: employee's perspective

Employee's costs and benefits included direct non-medical costs (i.e. the patient's out-of-pocket costs and costs in the domestic realm) and QALY health gains. Cumulated over twelve months the incremental benefits for the ECO group were €263 regarding non-medical costs and €696 due to QALY gains ($0.035 \times €20,000$). When solely focussing on the employee's out-of-pocket costs, then the incremental net-benefits of €263 are close the interventions cost of

1
2
3 €300, but this break-even is surrounded by uncertainty (bootstrapped $M=-37$; 95% CI= -
4 403~330; SE=187; $z=-0.20$; $p=0.845$). The benefits increase to a total of €959 when
5 including the value of QALY gains. Then the incremental net-benefits become €959-€300=
6 659, which is again surrounded by uncertainty (bootstrapped 95% CI=287~1,031; SE=190;
7 $z=3.47$; $p=0.001$).
8
9

10 11 **Cost-benefit analysis: societal perspective**

12 For the societal perspective we only included real economy euros, thus ignoring the value of
13 QALY gains. The difference between conditions of the cumulative benefits was €29,822-
14 €25,985=€3,837 in favour of the intervention condition (bootstrapped 95% CI=
15 -541~8,216; SE=2,233; $z=1.72$; $p=0.086$). Subtraction of the intervention costs of €300
16 yielded incremental net-benefits from a social perspective of €3,537 (bootstrapped 95% CI= -
17 875~7,950; SE=2,222; $z=1.57$; $p=0.116$). Break-even was achieved at seven months and the
18 return on investment was $3537/300=11,8$.
19
20
21
22
23

24 **Sensitivity analyses**

25 For the main analysis we used EM imputation; now we recomputed the estimates under
26 regression imputation (RI). Taking the societal perspective, the incremental net-benefits
27 became €3,423 (Bootstrapped 95% CI= -921~7,767; SE=2,216; $z=1.54$; $p=0.122$), which is
28 close to the EM-based analysis where the incremental net-benefits were estimated at a mean
29 of €3,537.
30
31
32
33

34
35 The incremental net-benefits in the main analyses were dominated by the costs offsets due to
36 reduced absenteeism, but these were based on self-reported data. Crosschecking the self-
37 reported data against administrative data derived from the registers of the occupational health
38 service or employer showed that the self-report data were more conservative than the
39 estimates based on administrative data (72 work days absent based on self-reported data
40 versus an average of 101 work days absent based on administrative data). When basing the
41 analysis on administrative data, the total cumulative incremental net-benefits became €5,758
42 (Bootstrapped 95% CI=-3,569~15,085; SE=4,759; $z=1.21$; $p=0.226$), which is higher by a
43 factor 1.63 than the corresponding estimate presented in the main analysis. The main analysis
44 thus represents a safer (lower) estimate.
45
46
47
48
49

50
51 Finally, we repeated the main analysis by replacing the total costs of the respondents with the
52 top 5% highest total costs due to absenteeism by the highest amount witnessed in the other
53 95% respondents. The top 5% outliers were mainly situated in the CAU condition, raising the
54 average costs for this group. The incremental net-benefits based on the trimmed costs
55
56
57
58
59
60

1
2
3 dropped from €3,537 to €2,928 (SE 95% CI= -1,143~7,000; SE=2,077; z=1.41; p=0.159),
4 which can be regarded as a more conservative lower bound.
5
6

7 **DISCUSSION**

8 **Principal findings**

9
10 This study was set out to evaluate the cost-effectiveness of an intervention that encourages
11 sick-listed employees with common mental disorders to make an early return to their work.
12 The economic evaluation was conducted as an incremental cost-benefit analysis and reports on
13 the incremental cost to benefit ratio, the return on investment, the break-even point, and the
14 incremental monetary net-benefits, as customary seen in business cases and investment
15 appraisals. These metrics were computed from various perspectives, such as the employer's
16 perspective, and those of the employee and the health care financier. The main findings can
17 now be summarised as follows:
18
19

- 20 • Taking the employer's perspective, the focus of the economic evaluation was placed on the
21 intervention costs and changes in productivity owing to changes in absenteeism and
22 presenteeism. Assuming that the employer would make the investment in the ECO
23 intervention of €300 per employee, the incremental net-benefits were €3,187 per employee
24 over a year. This was equivalent to a return on investment of €11 per invested Euro.
25 Benefits were largely stemming from reduced absenteeism and exceeded the investment
26 costs after six months.
27
- 28 • From the perspective of the health care payer the incremental net-benefits were negative,
29 amounting to additional costs of €213 per employee on average.
30
- 31 • As seen from the employee the net-benefits exceeded the costs by €659 when also valuing
32 the employee's QALY health gains. When excluding the QALY benefits, the incremental net-
33 benefits were slightly negative (€37).
34
35

36
37 From the societal perspective, the initial investment was also more than recouped. Considering
38 all costs and benefits, but ignoring the value of QALY gains, the incremental net-benefits were
39 €3,537, with a break-even point at 7 months. Every euro invested yielded €12. Trimming the
40 5% highest costs, mostly from the care as usual condition, reduced the incremental net-
41 benefits to €2,928.
42
43

44 **Limitations**

45 This study has several limitations, which are reported and discussed here.

- 46 • First, cost data are often non-normally distribution with a few people generating very high
47 costs. This results in large standard deviations in the costs estimates and less stable
48 estimates of average costs. In such a context it would require a very large sample size to
49 power the trial for testing economic hypotheses. However, our study was only powered to
50
51
52
53
54
55
56
57
58
59
60

1
2
3 test a difference in sickness absence duration. As a consequence, the wide 95% confidence
4 intervals indicate that the cost estimates are subject to much uncertainty. More specifically,
5 when trimming the highest 5% of the costs in one of our sensitivity analysis showed that
6 the incremental net-benefits became €2,928, which is 83% of the original estimate of
7 €3,537. This suggests that our study needs replication, preferably in a larger study.

- 10 • Second, loss-to follow up was substantial. To handle dropouts, missing data were imputed
11 using estimation maximization (EM). To ascertain the robustness of our findings we also
12 used regression imputation (RI). With RI we arrived at similar conclusions: €3,423 (versus
13 €3,537 under EM), attesting to the robustness in our findings. Nevertheless, selection bias
14 introduced by (selective) dropout cannot be ruled out completely and could have influenced
15 the outcomes that we obtained.
- 19 • Third, costs at baseline were higher in the ECO condition. We could have adjusted for the
20 baseline differences, but this would have led to even better outcomes in favour of the ECO
21 condition. Ignoring the baseline differences has therefore put our main analyses on a more
22 conservative footing.
- 25 • Fourth, the main driver of costs and benefits was absenteeism and in the main analysis
26 these were based on self-report. This may have introduced some recall bias, but self-
27 reports of absenteeism usually involve underreporting thus leading to conservative
28 outcomes. Nevertheless, we crosschecked the data with administrative data from the
29 registers of the occupational health service and employer. As expected, the benefits were
30 lower when based on self-reports than on administrative data.
- 34 • Fifth, it should be noted that the cost-benefit analysis did not include the future costs of
35 implementing the ECO intervention on a wider scale. As the main component is a low cost
36 self-help intervention (Return@Work) and the training of OPs only lasts a few hours, the
37 implementation costs are expected to be low, but should be considered when the
38 intervention is disseminated on a wider scale.
- 41 • Finally, the follow-up time is limited to 12 months. We do not know what the net-benefits
42 would be over a longer time span. However, costs differences were highest in the last
43 months. This may imply that a longer follow-up period would have seen more profitable
44 outcomes.

47 48 **Results in context**

49 Reviews about the effectiveness of psychological return to work interventions for employees
50 with mental health problems show mixed outcomes in reducing sickness absence and
51 promoting an earlier return to work.[12, 22] Moreover, only a few of the reviewed studies that
52 appeared to be effective report a full economic evaluation. Of these, none evaluated a guided
53 eHealth intervention for return to work. One study that is somewhat comparable with our
54 study is from Schene and colleagues. Schene et al describe the economic evaluation of an
55
56
57
58
59
60

1
2
3 intervention for employees with major depression, who were sick-listed for 10 weeks up to 2
4 years.[39] The experimental condition received occupational therapy in addition to usual
5 outpatient treatment for depression. Their intervention increased the number of hours worked
6 accumulating in a median economic gain of US\$4000–5000 per patient per year, which is in
7 line with our findings regarding the reduction in absenteeism. The study of Schene et al was
8 smaller (n=62), was directed at a more severely depressed population, and the intervention
9 was not delivered online but as an intensive face-to-face therapy consisting of 24 group
10 sessions and 15 individual sessions.

11
12 Lerner and colleagues evaluated a brief telephonic program to improve work functioning for
13 employees with major depressive disorder or dysthymia with an at-work productivity loss of at
14 least 5% in the past two weeks.[40] Compared to usual care, annualised cost savings
15 averaged at \$6042 per participant but these savings were extrapolated from a shorter (4
16 months) follow-up. These cost savings are higher than the cost-savings observed in our study.
17 Nonetheless, Lerner's et al. extrapolation from 4 to 12 months might have overstated the
18 savings if the treatment effect was not sustained.

19
20 Arends and colleagues evaluated the costs and benefits of a problem-solving intervention
21 provided by OPs to prevent recurrent sickness absence in workers with common mental
22 disorders.[41] Compared to care as usual the intervention was more effective but also more
23 expensive. From an employer's perspective the intervention showed no economic benefits,
24 which is in contrast to our study.

25
26 Finally, Noben and colleagues conducted a cost-benefit analysis from the employer's
27 perspective of a preventive intervention in the work setting among nurses with an elevated-
28 risk of mental complaints.[42] The authors concluded that the intervention was a good
29 investment as the net-benefits (stemming from reduced absenteeism and presenteeism) were
30 positive (€651) and the return on investment was €11. This return on investment is
31 comparable with ours. However, the results of our study are related to a preventive
32 intervention and can only be generalised to employees who have been sick-listed for 4-26
33 weeks, working in small- to medium-sized companies.

44 45 **Conclusions and implications**

46
47 In the Netherlands, employers have an incentive to invest in sickness management as they
48 have the responsibility to pay 70-100% of the salary of sick-listed employees for up to two
49 years. Employees who are on sickness absence have to visit an occupational physician, paid by
50 the employer within the first six weeks. Both the employee and employer have to agree on an
51 action plan. In this plan the responsibilities of both parties are defined to ensure a quick return
52 to work of the employee. In this context the ECO-intervention can be seen as an effective
53 intervention that, in addition, has a high probability of offering good value for money because
54 the initial investment (of €300) is more than recouped within a single year as seen from the
55
56
57
58
59
60

1
2
3 employer's perspective, while the employee derives benefits in the form of increased quality of
4 life when returning to work sooner rather than later. However, the wide 95% confidence
5 intervals require careful interpretation. This suggests that our study needs replication in a
6 larger study and preferably over a longer time span.
7
8
9

10 **Acknowledgements**

11 We acknowledge with many thanks Prof.dr. H Anema (VU University) for advice on the design
12 of the study, Dr. G. van Lomwel (ACHMEA/UWV) for advice on design of the study and
13 providing access to data, and Dr. M Blankers for help with statistical analyses.
14
15
16

17 **Contributors**

18 CFC initiated the collaborative clinical trial project. MZV, AB and CFC contributed to the design
19 of the study and obtained the funding. DV, MZV and CFC were responsible for the acquisition
20 of the data. SL and FS conducted the statistical analysis and drafted the manuscript, which all
21 authors critically revised. All authors read and approved the final manuscript. SL, FS and CFC
22 are guarantors.
23
24
25
26

27 **Funding**

28 This study was financially supported by The Netherlands Organization for Health Research and
29 Development (ZonMw) (grant number 171002403) and Achmea, a Dutch health insurance
30 company. The funding sources had no role in the data analysis and interpretation and in the
31 writing of this paper.
32
33
34
35

36 **Competing interests**

37 All authors have completed the ICMJE uniform disclosure form at
38 www.icmje.org/coi_disclosure.pdf and declare: financial support for the submitted work from
39 The Netherlands Organisation for Health Research and Development (ZonMw) and from
40 Achmea SZ; SL, DV, MZV, BB, FS report personal fees from employment at the Trimbos
41 institute, the Netherlands institute of mental health and addiction, a not-for-profit
42 organisation, CFC has received research grants from Eli Lilly outside the submitted work.
43
44
45
46
47

48 **Ethical approval**

49 The study protocol was approved by the Medical Ethics Committee of the University Medical
50 Center Utrecht, The Netherlands, in February 2011. All participants provided written informed
51 consent before taking part.
52
53
54
55
56
57
58
59
60

Transparency

The lead author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that and discrepancies from the study as planned (and if relevant, registered) have been explained.

Data sharing: No additional data

Copyright

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Legends of figures

Figure 1. Flowchart of the clusters and participants

References

1. Lerner D, Amick BC, Lee JC, et al. Relationship of employee-reported work limitations to work productivity. *Med Care* 2003;41(5):649–59. doi:10.1097/01.MLR.0000062551.76504.A9.
2. Adler DA, McLaughlin TJ, Rogers WH, et al. Job performance deficits due to depression. *Am J Psychiatry* 2006 Sep;163(9):1569–76. doi:10.1176/ajp.2006.163.9.1569.
3. Moncrieff J, Pomerleau J. Trends in sickness benefits in Great Britain and the contribution of mental disorders. *J Public Health Med* 2000;22(1):59–67. doi:10.1093/pubmed/22.1.59.
4. Shiels C, Gabbay MB, Ford FM. Patient factors associated with duration of certified sickness absence and transition to long-term incapacity. *Br J Gen Pract* 2004;54(499):86–91.
5. Cattrell A, Harris EC, Palmer KT, et al. Regional trends in awards of incapacity benefit by cause. *Occup Med (Lond)* 2011;61(3): 148–151. doi:10.1093/occmed/kqr008 [published Online First: 11 April 2011].

- 1
2
3 6. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases
4 and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease
5 Study 2010. *Lancet* 2012;380:2197-2223. doi:10.1016/S0140-6736(12)61689-4 [published
6 Online First: 22 February 2013].
7
8
- 9
10 7. de Graaf R, Tuithof M, van Dorsselaer S, et al. Sick leave due to psychological and physical
11 illnesses among employees: results of the 'Netherlands Mental Health Survey and Incidence
12 Study-2' (NEMESIS-2) [in Dutch: Verzuim door psychische en somatisch aandoeningen bij
13 werkenden: resultaten van de 'Netherlands Mental Health Survey and Incidence Study-2'
14 (NEMESIS-2)]. Utrecht: Trimbos-instituut 2011.
15
16
- 17
18 8. Lelliott P, Tulloch S, Boardman J, et al. Mental Health and Work. London: Cross Government
19 Health Work and Well-being Programme 2008.
20
21
- 22
23 9. Chisholm D, Sanderson K, Ayuso-Mateos JL, et al. Reducing the global burden of
24 depression. *Br J Psychiatry* 2004;184:393-403. doi:10.1192/bjp.184.5.393.
25
26
- 27
28 10. Harvey SB, Joyce S, Modini M, et al. Work and depression/anxiety disorders: a systematic
29 review of reviews. Melbourne, Australia: Beyondblue 2013.
30
31
- 32 11. Ejeby K, Savitskij R, Ost LG, et al. Symptom reduction due to psychosocial interventions is
33 not accompanied by a reduction in sick leave: results from a randomized controlled trial in
34 primary care. *Scand J Prim Health Care* 2014;32(2):67-72.
35 doi:10.3109/02813432.2014.909163 [published Online First: 17 April 2014].
36
37
- 38
39 12. Nieuwenhuijsen K, Faber B, Verbeek JH, et al. Interventions to improve return to work in
40 depressed people. *Cochrane Database Syst Rev* 2014;12:CD006237.
41 doi:10.1002/14651858.CD006237 [published Online First: 3 December 2014].
42
43
- 44
45 13. OECD (2014). Mental Health and Work: Netherlands, Mental Health and Work. Paris: OECD
46 Publishing. doi:10.1787/9789264223301-en.
47
48
- 49 14. van der Klink JJL. Richtlijn: Handelen van de bedrijfsarts bij werkenden met psychische
50 problemen. [Guideline: The management of mental health problems of workers by
51 occupational physicians] Eindhoven: NVAB [Netherlands Society of Occupational Medicine]
52 2000.
53
54
55
56
57
58
59
60

1
2
3 15. Rebergen DS, Bruinvels DJ, Bos CM, et al. Return to work and occupational physicians'
4 management of common mental health problems – process evaluation of a randomized
5 controlled trial. *Scand J Work Environ Health* 2010;36(6):488-498. doi:10.5271/sjweh.3084.
6
7

8
9 16. Rebergen D, Hoenen J, Heinemans A, et al. Adherence to mental health guidelines by
10 Dutch occupational physicians. *Occup Med (Lond)* 2006;56(7):461-468.
11 doi:10.1093/occmed/kql042 [published Online First: 16 June 2006].
12

13
14 17. Rebergen DS, Bruinvels DJ, Bezemer PD, et al. Guideline-based care of common mental
15 disorders by occupational physicians (CO-OP study): a randomized controlled trial. *J Occup
16 Environ Med* 2009;51(3):305-312. doi:10.1097/JOM.0b013e3181990d32.
17
18

19
20 18. Van der Feltz CM, Hoedeman R, de Jong FJ, et al. Faster return to work after psychiatric
21 consultation for sicklisted employees with common mental disorders compared to care as
22 usual. A randomized clinical trial. *Neuropsychiatr Dis Treat*. 2010;6:375-385.
23 doi:10.2147/NDT.S11832 [published Online First: 2 July 2010].
24
25

26
27 19. Vlasveld MC, van der Feltz-Cornelis CM, Adèr HJ, et al. Collaborative care for sick-listed
28 workers with major depressive disorder: a randomised controlled trial from the Netherlands
29 Depression Initiative aimed at return to work and depressive symptoms. *Occup Environ Med*
30 2013;70(4):223-230. doi:10.1136/oemed-2012-100793 [published Online First: 29 October
31 2012].
32
33

34
35 20. Volker D, Vlasveld MC, Anema JR, et al. Blended E-health module on return to work
36 embedded in collaborative occupational health care for common mental disorders: design of a
37 cluster randomized controlled trial. *Neuropsychiatr Dis Treat* 2013;9:529-537.
38 doi:10.2147/NDT.S43969 [published Online First: 19 April 2013].
39
40

41
42 21. Volker D, Zijlstra-Vlasveld MC, Anema JR, et al. Effectiveness of a Blended Web-Based
43 Intervention on Return to work for Sick-Listed Employees With Common Mental Disorders:
44 Results of a Cluster Randomized Controlled Trial. *J Med Internet Res* 2015;17(5):e116.
45 doi:10.2196/jmir.4097 [published Online First: 13 May 2015].
46
47

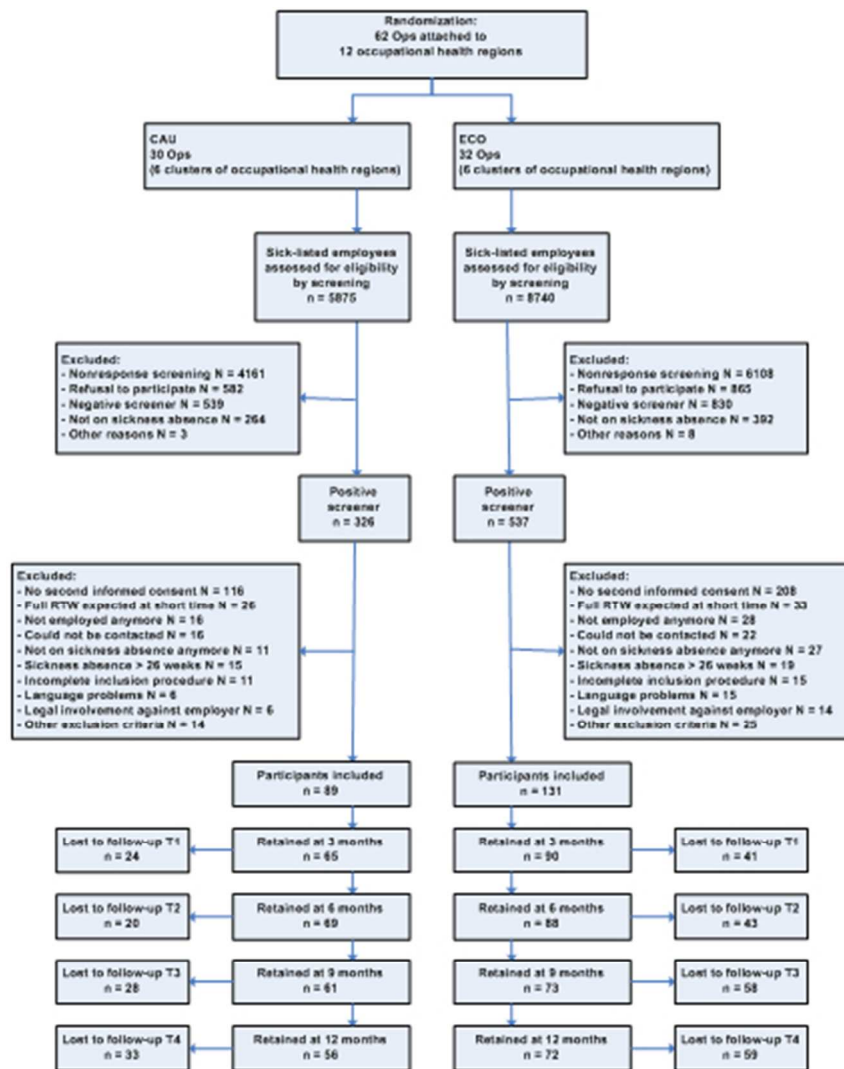
48
49 22. Arends I, Bruinvels DJ, Rebergen DS, et al. Interventions to facilitate return to work in
50 adults with adjustment disorders. *Cochrane database Syst Rev*. 2012;12:CD006389.
51 doi:10.1002/14651858.CD006389.pub2 [published Online First: 12 December 2012].
52
53
54
55
56
57
58
59
60

- 1
2
3 23. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity
4 measure. *J Gen Intern Med* 2001;16(9):606-613.
5 doi:10.1046/j.1525-1497.2001.016009606.x [published Online First: 20 December 2001].
6
7
8
9 24. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: validity of a new measure for
10 evaluating the severity of somatic symptoms. *Psychosom Med* 2002;64(2):258-266.
11 doi:10.1097/00006842-200203000-00008.
12
13
14 25. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized
15 anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166(10):1092-1097.
16 doi:10.1001/archinte.166.10.1092.
17
18
19
20 26. Nieuwenhuijsen K, Noordik E, van Dijk FJH, et al. Return to work perceptions and actual
21 return to work in workers with common mental disorders. *J Occup Rehabil*. 2013;23(2):290-9.
22 doi:10.1007/s10926-012-9389-6 [published Online First: 3 November 2012].
23
24
25
26 27. van Oostrom SH, Mechelen van MW, Terluin B, et al. A workplace intervention for sick-
27 listed employees with distress: results of a randomised controlled trial. *Occup*
28 *Environ Med* 2010;67(9):596-602. doi:10.1136/oem.2009.050849 [published Online First: 2
29 April 2010].
30
31
32
33 28. Volker D, Zijlstra-Vlasveld MC, Brouwers EPM, et al. Return-to-work self-efficacy and
34 actual return to work among long-term sick-listed employees. *J Occup Rehabil* 2015; 25
35 (2):423-341. doi:10.1007/s10926-014-9552-3 [published Online First: 30 October 2014].
36
37
38
39 29. Hakkaart-van Roijen L. Manual Trimbos/iMTA questionnaire for costs associated with
40 psychiatric illness (in Dutch). Rotterdam: Institute for Medical Technology Assessment 2002.
41
42
43
44 30. Euroqol Group. *Eq-5D User Guide*. Rotterdam, The Netherlands: Sanders Instituut, EUR
45 1995.
46
47
48 31. Lamers, L. M., McDonnell, J., Stalmeier, P. F. M., Krabbe, P. F. M., & Busschbach, J. J. V.
49 (2006). The Dutch tariff: results and arguments for an effective design for national EQ-5D
50 valuation studies. *Health Econ*, 15(10), 1121-32. doi:10.1002/hec.1124 [published Online
51 First: 19 June 2006].
52
53
54
55
56
57
58
59
60

- 1
2
3 32. Hakkaart L, Tan S, Bouwmans C. Manual for cost research. Methods and standard costs for
4 economic evaluations in healthcare (in Dutch). Rotterdam: Institute for Medical Technology
5 Assessment, Erasmus University Rotterdam 2010.
6
7
8
9 33. Zorginstituut Nederland (2014a). Dutch Health Care Insurance Board (in Dutch)
10 (<http://www.medicijnkosten.nl/>). Accessed 7 May 2014.
11
12
13 34. Zwaap J, Knies S, van der Meijden C, et al. Kosteneffectiviteit in de praktijk. Diemen:
14 Zorginstituut Nederland 2015.
15
16
17 35. Rice DP, Cooper BS. The economic value of human life. *Am J Public Health Nations Health*
18 1967;57:1954–1966. doi: 10.2105/AJPH.57.11.1954.
19
20
21 36. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for
22 reporting parallel group randomised trials. *BMJ* 2010;340:c332. doi:10.1136/bmj.c332.
23
24
25 37. Campbell MK, Piaggio G, Elbourne DR, et al. Consort 2010 statement: extension to cluster
26 randomised trials. *BMJ* 2012;345:e5661. doi:10.1136/bmj.e5661.
27
28
29 38. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation
30 Reporting Standards (CHEERS) statement. *BJOG* 2013;120:765-770. doi:10.1136/bmj.f1049.
31
32
33 39. Schene AH, Koeter MW, Kikkert MJ, et al. Adjuvant occupational therapy for work-related
34 major depression works: randomized trial including economic evaluation. *Psychol*
35 *Med* 2007;37:351–362. doi:dx.doi.org/10.1017/S0033291706009366 [published Online First:
36 20 November 2006].
37
38
39 40. Lerner D, Adler D, Hermann RC, et al: Impact of a work-focused intervention on the
40 productivity and symptoms of employees with depression. *J Occup Environ Med* 54:128–135,
41 2012. doi:10.1097/JOM.0b013e31824409d8 [published Online First: 1 March 2015].
42
43
44 41. Arends I, Bültmann U, van Rhenen W, et al. Economic evaluation of a problem solving
45 intervention to prevent recurrent sickness absence in workers with common mental disorders.
46 *PLoS One* 2013;8:e71937. doi:10.1371/journal.pone.0071937 [published Online First: 12
47 August 2013].
48
49
50 42. Noben C, Evers S, Nieuwenhuijsen K, et al. Protecting and promoting mental health of
51 nurses in the hospital setting: is it cost-effective from an employer's perspective?
52
53
54
55
56
57
58
59
60

1
2
3 *Int J Occup Med Environ Health* 2015;28(5). doi:10.13075/ijomeh.1896.00465.
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only



Flowchart of the participants



CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

| Section/item | Item No | Recommendation | Reported on page No/line No |
|---------------------------------|---------|--|-----------------------------|
| Title and abstract | | | |
| Title | 1 | Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared. | 3 |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | 3 |
| Introduction | | | |
| Background and objectives | 3 | Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions. | 4,5 |
| Methods | | | |
| Target population and subgroups | 4 | Describe characteristics of the base case population and subgroups analysed, including why they were chosen. | 6 |
| Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | 6 |
| Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | 9 |
| Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen. | 7 |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | 8 |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | 8 |
| Choice of health outcomes | 10 | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed. | 8/9 |
| Measurement of effectiveness | 11a | <i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. | 5-7 |



| | | | | |
|----|-------------------------|-----|---|-------|
| 1 | | 11b | <i>Synthesis-based estimates:</i> Describe fully the methods used for | |
| 2 | | | identification of included studies and synthesis of clinical | |
| 3 | | | effectiveness data. | N.A. |
| 4 | | | | |
| 5 | Measurement and | 12 | If applicable, describe the population and methods used to | |
| 6 | valuation of preference | | elicit preferences for outcomes. | |
| 7 | based outcomes | | | N.A. |
| 8 | | | | |
| 9 | Estimating resources | 13a | <i>Single study-based economic evaluation:</i> Describe approaches | |
| 10 | and costs | | used to estimate resource use associated with the alternative | |
| 11 | | | interventions. Describe primary or secondary research methods | |
| 12 | | | for valuing each resource item in terms of its unit cost. | |
| 13 | | | Describe any adjustments made to approximate to opportunity | |
| 14 | | | costs. | 7,8 |
| 15 | | | | |
| 16 | | 13b | <i>Model-based economic evaluation:</i> Describe approaches and | |
| 17 | | | data sources used to estimate resource use associated with | |
| 18 | | | model health states. Describe primary or secondary research | |
| 19 | | | methods for valuing each resource item in terms of its unit | |
| 20 | | | cost. Describe any adjustments made to approximate to | |
| 21 | | | opportunity costs. | N.A. |
| 22 | | | | |
| 23 | Currency, price date, | 14 | Report the dates of the estimated resource quantities and unit | |
| 24 | and conversion | | costs. Describe methods for adjusting estimated unit costs to | |
| 25 | | | the year of reported costs if necessary. Describe methods for | |
| 26 | | | converting costs into a common currency base and the | |
| 27 | | | exchange rate. | 8 |
| 28 | | | | |
| 29 | Choice of model | 15 | Describe and give reasons for the specific type of decision- | |
| 30 | | | analytical model used. Providing a figure to show model | |
| 31 | | | structure is strongly recommended. | N.A. |
| 32 | | | | |
| 33 | Assumptions | 16 | Describe all structural or other assumptions underpinning the | |
| 34 | | | decision-analytical model. | N.A. |
| 35 | | | | |
| 36 | Analytical methods | 17 | Describe all analytical methods supporting the evaluation. This | |
| 37 | | | could include methods for dealing with skewed, missing, or | |
| 38 | | | censored data; extrapolation methods; methods for pooling | |
| 39 | | | data; approaches to validate or make adjustments (such as half | |
| 40 | | | cycle corrections) to a model; and methods for handling | |
| 41 | | | population heterogeneity and uncertainty. | 9,10 |
| 42 | | | | |
| 43 | Results | | | |
| 44 | Study parameters | 18 | Report the values, ranges, references, and, if used, probability | |
| 45 | | | distributions for all parameters. Report reasons or sources for | |
| 46 | | | distributions used to represent uncertainty where appropriate. | |
| 47 | | | Providing a table to show the input values is strongly | |
| 48 | | | recommended. | 10-15 |
| 49 | | | | |
| 50 | Incremental costs and | 19 | For each intervention, report mean values for the main | |
| 51 | outcomes | | categories of estimated costs and outcomes of interest, as well | |
| 52 | | | as mean differences between the comparator groups. If | |
| 53 | | | applicable, report incremental cost-effectiveness ratios. | 10-15 |
| 54 | | | | |
| 55 | Characterising | 20a | <i>Single study-based economic evaluation:</i> Describe the effects | |
| 56 | uncertainty | | of sampling uncertainty for the estimated incremental cost and | |
| 57 | | | incremental effectiveness parameters, together with the impact | 12-14 |
| 58 | | | | |
| 59 | | | | |
| 60 | | | | |

| | | | |
|--|-----|--|-------|
| | | of methodological assumptions (such as discount rate, study perspective). | |
| | 20b | <i>Model-based economic evaluation</i> : Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | N.A. |
| Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | N.A. |
| Discussion | | | |
| Study findings, limitations, generalisability, and current knowledge | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | 15-18 |
| Other | | | |
| Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | 18 |
| Conflicts of interest | 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations. | 18 |

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

The citation for the CHEERS Task Force Report is:
 Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. *Value Health* 2013;16:231-50.

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

| Section/Topic | Item No | Standard Checklist item | Extension for cluster designs | Page No * |
|----------------------------------|---------|--|---|-----------|
| Title and abstract | | | | |
| | 1a | Identification as a randomised trial in the title | Identification as a cluster randomised trial in the title | 3 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) ^{1,2} | See table 2 | 3 |
| Introduction | | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | Rationale for using a cluster design | 4,5 |
| | 2b | Specific objectives or hypotheses | Whether objectives pertain to the cluster level, the individual participant level or both | 5 |
| Methods | | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | Definition of cluster and description of how the design features apply to the clusters | 5 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | | N/A |
| Participants | 4a | Eligibility criteria for participants | Eligibility criteria for clusters | 6 |
| | 4b | Settings and locations where the data were collected | | 6 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | Whether interventions pertain to the cluster level, the individual participant level or both | 7 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and | Whether outcome measures pertain to the cluster level, the individual participant level or both | 7/8 |

| | | | | |
|---|-----|---|---|-----|
| | | when they were assessed | | |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | | N/A |
| Sample size | 7a | How sample size was determined | Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or <i>k</i>), and an indication of its uncertainty | N/A |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | | N/A |
| Randomisation: | | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | | 6 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | Details of stratification or matching if used | 5/6 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both | 5/6 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | Replace by 10a, 10b and 10c | 6 |
| | 10a | | Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions | |
| | 10b | | Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete | |

| | | | | |
|---|-----|--|---|---------|
| | | | enumeration, random sampling) | |
| | 10c | | From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation | |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | | 6 |
| | 11b | If relevant, description of the similarity of interventions | | N/A |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | How clustering was taken into account | 9/10 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | | 10 |
| Results | | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome | 6/10/11 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | For each group, losses and exclusions for both clusters and individual cluster members | 10/11 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | | 6 |
| | 14b | Why the trial ended or was stopped | | N/A |
| Baseline data | 15 | A table showing baseline demographic and clinical | Baseline characteristics for the individual and cluster levels as | Table 1 |

| | | | | |
|--------------------------------|-----|---|--|-------|
| | | characteristics for each group | applicable for each group | |
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | For each group, number of clusters included in each analysis | 6/9 |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome | 11-14 |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | | N/A |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | | 14/15 |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms ³) | | N/A |
| Discussion | | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | | 15/16 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | Generalisability to clusters and/or individual participants (as relevant) | 17 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | | 16/17 |
| Other information | | | | |
| Registration | 23 | Registration number and | | 5/6 |

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

| | | |
|-----------------|----|---|
| | | name of trial registry |
| Protocol | 24 | Where the full trial protocol can be accessed, if available |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders |

** Note: page numbers optional depending on journal requirements*

For peer review only

Table 2: Extension of CONSORT for abstracts^{1,2} to reports of cluster randomised trials

| Item | Standard Checklist item | Extension for cluster trials |
|---------------------------|---|--|
| Title | Identification of study as randomised | Identification of study as cluster randomised |
| Trial design | Description of the trial design (e.g. parallel, cluster, non-inferiority) | |
| Methods | | |
| Participants | Eligibility criteria for participants and the settings where the data were collected | Eligibility criteria for clusters |
| Interventions | Interventions intended for each group | |
| Objective | Specific objective or hypothesis | Whether objective or hypothesis pertains to the cluster level, the individual participant level or both |
| Outcome | Clearly defined primary outcome for this report | Whether the primary outcome pertains to the cluster level, the individual participant level or both |
| Randomization | How participants were allocated to interventions | How clusters were allocated to interventions |
| Blinding (masking) | Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment | |
| Results | | |
| Numbers randomized | Number of participants randomized to each group | Number of clusters randomized to each group |
| Recruitment | Trial status ¹ | |
| Numbers analysed | Number of participants analysed in each group | Number of clusters analysed in each group |
| Outcome | For the primary outcome, a result for each group and the estimated effect size and its precision | Results at the cluster or individual participant level as applicable for each primary outcome |
| Harms | Important adverse events or side effects | |
| Conclusions | General interpretation of the results | |
| Trial registration | Registration number and name of trial register | |
| Funding | Source of funding | |

¹ Relevant to Conference Abstracts

REFERENCES

- 1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283
- 2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20
- 3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

BMJ Open

Return-to-work intervention versus usual care for sick-listed employees: health-economic investment appraisal alongside a cluster randomised trial

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2017-016348.R1 |
| Article Type: | Research |
| Date Submitted by the Author: | 15-May-2017 |
| Complete List of Authors: | Lokman, Suzanne; Trimbos-institute, Public Mental Health Volker, Danielle; Trimbos-institute Zijlstra-Vlasveld, Moniek; Trimbos-institute, Public Mental Health Brouwers, Evelien; Tilburg University Tilburg School of Social and Behavioral Sciences Boon, Brigitte; Trimbos-institute, Center of Innovation Beekman, Aartjan; EMGO Institute for Health and Care Research; VU University Medical Center Amsterdam, Department of Psychiatry Smit, Filip; Trimbos-institute, Public Mental Health; VU University Medical Centre, Department of Epidemiology and Biostatistics Van der Feltz-Cornelis, Christina; 7GGZ GGZ Breburg, TopClinical Centre for Body, Mind and Health; Tilburg University Tilburg School of Social and Behavioral Sciences, Tranzo |
| Primary Subject Heading: | Occupational and environmental medicine |
| Secondary Subject Heading: | Health economics |
| Keywords: | mental disorder, absenteeism, return to work, eHealth, cost-benefit, occupational health |
| | |

SCHOLARONE™
Manuscripts

1
2
3 1 **TITLE PAGE**

4
5 2
6 3 **Return-to-work intervention versus usual care for sick-listed employees: health-**
7 4 **economic investment appraisal alongside a cluster randomised trial**

8
9 5
10 6 Suzanne Lokman, Danielle Volker, Moniek C Zijlstra-Vlasveld, Evelien PM Brouwers, Brigitte
11 7 Boon, Aartjan TF Beekman, Filip Smit, Christina M van der Feltz-Cornelis

12 8
13 9 Trimbos-institute, Netherlands institute of mental health and addiction, Department of Public
14 10 Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands, Maastricht University,
15 11 Department of Health Services Research, CAPHRI School of Public Health and Primary Care, PO
16 12 Box 616, 6200 MD Maastricht, The Netherlands Suzanne Lokman
17 13 economist

18 14 Trimbos-institute (Netherlands institute of mental health and addiction), Department of Public
19 15 Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands, Tilburg University, School of
20 16 Social and Behavioral Sciences, Department Tranzo, PO Box 90153, 5000 LE Tilburg, The
21 17 Netherlands Daniëlle Volker
22 18 psychologist

23 19 Trimbos-institute, Netherlands institute of mental health and addiction, Department of Public
24 20 Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands Moniek C Zijlstra-Vlasveld
25 21 psychologist

26 22 Tilburg University, School of Social and Behavioral Sciences, Department Tranzo, PO Box
27 23 90153, 5000 LE Tilburg, The Netherlands Evelien P.M. Brouwers
28 24 psychologist

29 25 Trimbos-institute, Netherlands institute of mental health and addiction, Department of Public
30 26 Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands Brigitte Boon
31 27 head of Center of Innovation

32 28 Department of Psychiatry and Amsterdam Public Health research institute, VU University
33 29 Medical Center, AJ Ernststraat 1187,1081 HL Amsterdam, The Netherlands Aartjan TF
34 30 Beekman

35 31 professor of psychiatry

36 32 Trimbos-institute, Netherlands institute of mental health and addiction, Department of Public
37 33 Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands, Department of Clinical, Neuro
38 34 and Developmental Psychology, and Department of Epidemiology and Biostatistics, Amsterdam
39 35 Public Health research institute, VU University Medical Center, Van der Boechorststraat 1, 1081
40 36 BT Amsterdam, The Netherlands Filip Smit
41 37 professor of public mental health
42 38

1
2
3 1 Tilburg University, School of Social and Behavioral Sciences, Department Tranzo, PO Box
4 2 90153, 5000 LE Tilburg, The Netherlands, Clinical Centre of excellence for Body Mind and
5 3 Health, GGz Breburg, PO Box 90153, 5000 LE Tilburg, The Netherlands Christina M. van der
6 4 Feltz-Cornelis
7 5 professor of social psychiatry
8
9
10 6

11 7 Correspondence to: slokman@trimbos.nl
12 8

13 9 Key words: mental disorders, absenteeism, return to work, eHealth, cost-benefit, occupational
14 10 health

15 11 Word count: 5252; Number of figures: 1; Number of tables: 4; Number of references: 45

16 12 Number of supplementary files for online only publication: 0
17 13
18 14

1
2
3 1 **Return-to-work intervention versus usual care for sick-listed employees: health-**
4 2 **economic investment appraisal alongside a cluster randomised trial**

5
6 3 **ABSTRACT**

7
8 4
9 5 **OBJECTIVE:** To evaluate the health-economic costs and benefits of a guided eHealth
10 6 intervention (ECO) encouraging sick-listed employees to a faster return to work.
11 7

12 8
13 9 **DESIGN:** A 2-armed cluster randomised trial with occupational physicians (OPs) (n=62),
14 10 clustered and randomised by region into an experimental and a control group, to conduct a
15 11 health-economic investment appraisal. Online self-reported data were collected from
16 12 employees at baseline, after 3, 6, 9 and 12 months.
17 13

18 14
19 15 **SETTINGS:** Occupational health care in the Netherlands.
20 16

21 17
22 18
23 19 **PARTICIPANTS:** Employees from small-sized and medium-sized companies (≥ 18 years),
24 20 sick-listed between 4 and 26 weeks with (symptoms of) common mental disorders visiting
25 21 their OP.
26 22

27 23
28 24 **INTERVENTIONS:** In the intervention group, employees (N=131) received an eHealth module
29 25 aimed at changing cognitions regarding return to work, while OPs were supported by a
30 26 decision aid for treatment and referral options. Employees in the control condition (N=89)
31 27 received usual sickness guidance.
32 28

33 29
34 30 **OUTCOMES MEASURES:** Net-benefits and return on investment based on absenteeism,
35 31 presenteeism, health care use, and quality adjusted life years (QALYs) gained.
36 32

37 33
38 34 **RESULTS:** From the employer's perspective, the incremental net-benefits were €3,187 per
39 35 employee over a single year, representing a return of investment of €11 per invested Euro,
40 36 with a break-even point at six months. The economic case was also favourable from the
41 37 employee's perspective, partly because of QALY health gains. The intervention was costing
42 38 €213 per employee from a health service financier's perspective. The incremental net-benefits
43 39 from a social perspective were €4,233. This amount dropped to €3,616 in the sensitivity
44 40 analysis trimming the 5% highest costs.
45 41

46 42
47 43 **CONCLUSIONS:** The data suggest that the ECO intervention offers good value for money for
48 44 virtually all stakeholders involved, because initial investments were more than recouped within
49 45 a single year. The sometimes wide 95% confidence intervals suggest that the costs and
50 46 benefits are not always very precise estimates and real benefits could vary considerably.
51 47
52 48
53 49
54 50
55 51
56 52
57 53
58 54
59 55
60 56

1
2
3 1
4 2 **TRIAL REGISTRATION:** Netherlands Trial Register NTR2108
5
6 3
7 4

8 5 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
9 6

- 10 7
- 11 8 • This study adds to the only few available studies that present a trial-based investment appraisal of the economic costs and benefits of a return to work intervention for sick-listed employees
 - 12 9 • The trial was only powered to test a difference in sickness absence duration and not for testing economic hypotheses.
 - 13 10 • The follow-up time is limited to 12 months.
- 14 11
15 12
16 13
17 14
18 15
19 16
20 17
21 18
22 19
23 20
24 21
25 22
26 23
27 24
28 25
29 26
30 27
31 28
32 29
33 30
34 31
35 32
36 33
37 34
38 35
39 36
40 37
41 38
42 39
43 40
44 41
45 42
46 43
47 44
48 45
49 46
50 47
51 48
52 49
53 50
54 51
55 52
56 53
57 54
58 55
59 56
60 57

102 15 **INTRODUCTION**
103 16

104 17 Long-term sickness absence has a significant economic impact, largely due to the substantial productivity losses.[1, 2] Mental disorders are a leading cause of sickness absence,[3-6] which is not without economic ramifications.[7] Common mental disorders, specifically depression and anxiety, are the most prevalent in the workforce.[8]

105 22 For the treatment of common mental disorders a range of psychological and pharmaceutical interventions have been shown to be effective and cost-effective.[9, 10] However, symptomatic recovery does not automatically reduce sickness absence.[10-12] To improve occupational outcomes it is also important to pay attention to return to work during treatment.

106 27 In the Netherlands, treatment and sickness certification are separated from each other in social security legislation. Occupational physicians (OPs) play a central role in the sickness guidance of workers by making a problem analysis and giving advice on a return to work plan, whereas treatment is provided by the mental health sector. The legislation was introduced to protect the worker's privacy and to the possibility for the worker to maintain a confidential relationship with the curative physician.[13, 14] A guideline has been developed to suggest directions to OPs to better assist employees with mental health problems in the return to work process. According to this guideline, the OPs need to closely monitor both the mental health problems and the level of functioning. When recovery is slow or hampered, they can consult or refer to a psychiatrist, a psychologist or a social worker.[15] A study of Rebergen and colleagues suggested that better adherence to the guideline is associated with earlier return to work.[16] However, in practice, adherence appears to be far from optimal,[17, 18] and there is often a lack of cooperation between the OPs and treatment providers in the mental health

1
2
3 1 sector. Several attempts have been made to bridge this gap. One study about the effect of
4 2 psychiatric consultation for OPs assisting sick-listed employees did provide results in terms of
5 3 earlier return to work.[19] However, this study was small. Another study evaluating active
6 4 treatment by an OP within a collaborative care arrangement did improve depressive
7 5 symptoms, but failed to speed up return to work.[20] It appeared that OPs need support in
8 6 helping sick-listed employees change their attitude towards resuming work and that OPs
9 7 should monitor symptom improvement and work performance in a more systematic manner.
10 8

11 9 To overcome these problems and to better manage the return to work of sick-listed employees
12 10 with (symptoms of) common mental disorders, the "E-health module embedded in
13 11 Collaborative Occupational health care" (ECO) intervention was developed. The ECO
14 12 intervention was designed to promote return to work by improving work functioning in
15 13 employees, providing a decision aid for the OP who gives guidance to the employee, and by
16 14 including the opportunity for psychiatric consultation to the OP.[21]
17 15

18 16 The results of a recent trial showed that ECO led to an earlier return to work than usual care
19 17 (mean duration of 50 days in the ECO group versus 77 days in the CAU group) and higher
20 18 remission rates of common mental disorder after 9 months in a group of sick-listed employees
21 19 with (symptoms of) mental disorders.[22]
22 20

23 21 Taking the economic perspective, we expect that the ECO intervention is cost-effective as seen
24 22 from the employer's viewpoint, because ECO is a low cost self-help intervention with a limited
25 23 amount of support from the OP and appears to be effective in reducing absenteeism. There is
26 24 less certainty how cost-effective the intervention would be as seen from the perspective of the
27 25 sick-listed employees and the health care financier (i.e. health care insurance company in the
28 26 Dutch context). Therefore, this study conducts a costs-benefit analysis of the ECO intervention
29 27 from all three stakeholders' viewpoints, and combines these in an overarching societal
30 28 perspective. These analyses are important because very few trial-based economic evaluations
31 29 have been conducted with regard to return-to-work interventions for sick-listed employees
32 30 with (symptoms of) common mental disorders.[12, 23]
33 31

34 32 **METHOD**

35 34 **Study design**

36 35 The ECO study was designed as a 2-armed cluster randomised controlled trial, with
37 36 randomisation at the level of the OP. OPs were either randomised to usual care alone or usual
38 37 care plus the ECO intervention. The Netherlands Organization for Health Research and
39 38 Development funded the study (grant number 171002403 ZonMw Doelmatigheid) together
40 41
41 42
42 43
43 44
44 45
45 46
46 47
47 48
48 49
49 50
50 51
51 52
52 53
53 54
54 55
55 56
56 57
57 58
58 59
59 60

1
2
3 1 with Achmea, a Dutch insurance company. The Medical Ethics Committee of the University
4 2 Medical Center Utrecht approved the study protocol in 2011, and the trial was registered at the
5 3 Netherlands Trial Register (NTR) under number 2108. The design of the study is described in
6 4 detail elsewhere.[21, 22] Here, we provide a brief summary of the main characteristics and
7 5 focus on the economic aspects.
8
9
10 6

7 **Randomisation**

13 8 To prevent contamination, cluster randomisation took place at the level of the OPs working in
14 9 the same region across a total of twelve regions. An independent statistician randomised six
15 10 regions to the ECO condition and the remainder to the control condition using computer-
16 11 generated randomisation. Since the OPs had to offer the intervention, they could not be
17 12 blinded for randomisation. The researchers and participants were informed about the allocation
18 13 after the randomisation procedure.
19
20
21
22 14

23 15 **Participants**

24 16 Participants were recruited from July 2011 to January 2013 from all-cause sick-listed
25 17 employees working at small-sized and medium-sized companies in the Netherlands who visited
26 18 an OP. To be eligible for inclusion the employees had to be at least 18 years of age and on
27 19 sickness absence between 4 and 26 weeks. This time window was chosen to avoid including
28 20 employees with spontaneous recovery and to increase the probability of employees ever
29 21 returning to work.[24] In addition, the employees needed to have a score ≥ 10 on either the
30 22 depression or the somatization scale of the Patient Health Questionnaire (PHQ-9),[25, 26] or
31 23 the Generalized Anxiety Disorder questionnaire (GAD-7).[27] Exclusion criteria were (1) poor
32 24 command of the Dutch language, (2) pregnancy, (3) not having access to the Internet, (4)
33 25 being involved in a legal action against the employer.
34
35
36
37
38
39
40
41 26

42 27 **Procedure**

43 28 Initially an independent statistician randomised 12 regions to either CAU (6 regions with 30
44 29 OPs) or ECO (6 regions with 32 OPs) by using a computer algorithm. Within the cluster of CAU
45 30 regions 5,875 sick-listed employees were screened for eligibility resulting in 326 screen-
46 31 positives. In the cluster of ECO regions, 537 screen-positives were obtained from 8740 sick-
47 32 listed employees. Of these, 89 consenting participants received sickness guidance from OPs
48 33 who were randomised to CAU and 131 participants from OPs in the ECO cluster. The unequal
49 34 distribution of participants over the conditions was due to the cluster randomisation of the OPs.
50 35 Participants received measurements at baseline and at 3, 6, 9 and 12 months post baseline.
51 36 Dropout occurred in both conditions (see figure 1).
52
53
54
55
56
57
58
59
60

38 Figure 1. Flowchart of the participants

1

Intervention

ECO consists of 2 components: (1) the eHealth module Return@Work for the employee and (2) an email-based decision-aid to support the OP. Return@Work is aimed at improving the self-efficacy of employees and promoting the employee's intention to return to work. Recent studies have shown that these factors are predictors of actual work resumption.[28-30] The decision-aid provides the OPs with advice regarding treatment and referral options based on the employee's outcome monitoring in Return@Work.

9

The eHealth module starts with an assessment questionnaire. Depending on the results of the questionnaire regarding symptoms and cognitions about return to work of the individual employee, Return@Work presented specific modules and sessions. As a consequence, the amount of modules and sessions offered to the employees differed. In total, Return@Work included 5 modules composed of 16 sessions, covering: 1) psycho-education, 2) cognitions regarding return to work while having symptoms (based on principles of cognitive behavioural therapy), 3) problem solving skills, 4) pain and fatigue management and reactivation, and 5) relapse prevention. The employees went through the modules independently, but had the possibility to discuss Return@Work modules and assignments with the OP. The OPs were requested to inquire about the employee's progress in the eHealth module and to provide support if necessary during their regular face-to-face contacts with the employee. Periodic visits between the employee and the OP are part of the guidelines of the Dutch Board for Occupational Medicine (NVAB),[15] to which all OPs were required to adhere.

23

Besides the modules, Return@Work also contained a monitor of functioning and symptoms on a regular basis. This monitor was used for the second component of ECO, a decision aid to support OPs in the sickness guidance of employees. Based on the outcomes of the monitor in Return@Work the OPs received automated email messages with advice for next steps in collaborative care. In addition, the decision aid gave OPs the option to consult a psychiatrist in case insufficient progress was made. The OPs in the experimental condition received a 4-hour training about ECO.

31

In the control condition the employees received usual sickness guidance. The guidelines of the NVAB were used as a protocol.[15] As there is a lack of adherence to the guidelines,[17,18] actual care was assessed with a questionnaire by all of the participating employees.

35

Outcome measures

Participants filled in the Medical Technology Assessment Cost Questionnaire for Psychiatry (TiC-P),[31] which amongst health care use also measures absenteeism from work, which is

58

59

60

1
2
3 1 the main outcome variable of this study. The TiC-P is based on self-report and to crosscheck
4 2 the number of work days lost to absenteeism we compared the self-reports with administrative
5 3 data (see Sensitivity Analysis below). Total follow-up time was 12 months with measurements
6 4 at baseline and after 3, 6, 9 and 12 months. Finally, health gains in terms of quality adjusted
7 5 life years (QALYs) were assessed using the EuroQoL-5D-3L,[32] with the Dutch tariff.[33]
8 6

7 **Resource use and costing**

8 Cost data were collected using the TiC-P, including (1) direct medical costs, including the costs
9 10 of medication, (2) direct non-medical costs (patients' out-of-pocket costs for trips to health
11 11 services), (3) costs stemming from productivity losses owing to absenteeism and
12 12 presenteeism, and (4) costs that occurred in the domestic realm (help for housekeeping from
13 13 family, friends or hired people). Standard costs, expressed in euro (€), were indexed for the
14 14 reference year 2011 using the consumer price index from Statistics Netherlands. Costs were
15 15 not discounted because the follow-up period did not exceed one year.

16 **Computation of costs**

17 The set costs of the ECO intervention are €300 per user, which is its current (post trial) rate.
18 18 Direct medical costs are limited to mental health service use. The medical costs were
19 19 computed by multiplying the number of health service units (sessions, visits, hospital days)
20 20 with their standard full economic cost price.[34] Only medication costs for mental problems
21 21 were included in the economic analysis. For every type of drug (e.g. antidepressants,
22 22 benzodiazepines, antipsychotics, hypnotics) an average cost price was calculated based on the
23 23 cost prices per standard daily dose of three drugs most often prescribed to the participants as
24 24 reported in the Pharmaceutical Compass,[35] while taking into account the GP's prescription
25 25 costs, the pharmacist's dispensing costs and the pharmacist's claw back as per the guideline
26 26 for cost computations in health care.[34]
27 27

28 The direct non-medical costs consisted of the travel costs that participants had to make to visit
29 29 OPs and health services. These costs were calculated as the average distance to the specific
30 30 health service provider multiplied by the costs per km (€0.21) plus parking costs (€3.11) per
31 31 hour. To the direct non-medical costs we added the costs of (informal) caregivers (e.g. family
32 32 and friends) due to the employee's reduced functionality at home, computed by multiplying the
33 33 number of hours by €12.96.
34 34

35 In the Netherlands QALY health gains are valued at €50,000 per QALY with a range between
36 36 €20,000 and €80,000.[36] We used the lower bound of €20,000 to conduct our analysis under
37 37 conservative assumptions.
38 38

1
2
3 1 Productivity losses comprised the costs of lost workdays due to absenteeism and the costs of
4 2 inefficiency while at work (presenteeism). We used the human capital method to value the
5 3 productivity costs.[37] In the case of absenteeism, this method multiplies the number of days
6 4 absent by the gender and age-specific average gross wages per employee, as per the Dutch
7 5 guideline for health economic evaluation.[34] To assess the costs of presenteeism we used the
8 6 number of days actually worked when ill multiplied by a self-reported inefficiency score. This
9 7 score ranged from 0 (as effective as in good health) to 1 (totally ineffective). Again, the
10 8 gender and age-specific average gross wages were used to compute the costs of presenteeism.
11 9 To illustrate, if an employee reported an inefficiency score of 0.50 for 7 working days then we
12 10 assumed that 3.5 working days have been lost due to presenteeism.
13
14
15
16
17
18
19

20 12 **Analyses**

21 13 Following recommendations from the CONSORT and CHEERS statements,[38-40] analyses
22 14 were conducted in agreement with the intention to treat principle. Therefore all participants as
23 15 randomised were retained in the analysis and missing observations due to dropout were
24 16 imputed. For imputation we used both the estimation-maximisation (EM) algorithm as
25 17 implemented in SPSS for the main analysis, and regression imputation (RI) as implemented in
26 18 Stata for the sensitivity analysis (see below). In both imputation strategies we used predictors
27 19 of outcomes (costs and QALYs) and predictors of dropout (age, gender, partner status, country
28 20 of birth, number of work loss days). Predictors of the outcomes were included to increase
29 21 precision in the imputed values, predictors of dropout were incorporated to tackle selection-
30 22 bias, if any, and to meet the missing at random (MAR) assumption underlying most imputation
31 23 techniques.
32
33
34
35
36
37

38 25 The economic evaluation was conducted as an incremental cost-benefit analysis, because the
39 26 primary outcome (duration of sick leave) could directly be expressed in terms of monetary
40 27 benefits. The costs and benefits were calculated at baseline, 3, 6, 9 and 12 months in the ECO
41 28 and CAU conditions. The costs in the intermediate months were linearly interpolated. This
42 29 allowed mapping the monthly cash flows of costs and benefits over the full 12-month period.
43 30 The cash flows were computed from four perspectives: (1) the employer's perspective
44 31 focussing on the net-benefits from greater productivity via lesser absenteeism and lesser
45 32 presenteeism; (2) the health care payer's perspective (in the Netherlands: health care
46 33 insurers) focussing on the direct medical costs due to health service use, including the costs of
47 34 medication, (3) the employee's perspective focussing on QALY health gains, fewer out-of-
48 35 pockets costs and less informal care from family members or friends. Finally, we included the
49 36 societal perspective (4), including all costs and benefits, regardless of who incurs costs or
50 37 receives benefits.
51
52
53
54
55
56
57
58
59
60

1
2
3 1 The monthly cash flows were used to compute the cumulative costs and cumulative monetary
4 2 benefits over the full twelve months. Incremental costs, incremental benefits and incremental
5 3 net-benefits were obtained by comparing ECO intervention with CAU. These are the main
6 4 outcomes of the economic analysis alongside metrics such as the break-even point and the
7 5 return on investment (ROI).
8
9

10 6
11 7 For assessing the incremental net-benefits we relied on non-parametric bootstrapping (2,500
12 8 replications) since costs are non-normally distributed. Statistics such as mean costs, 95%
13 9 confidence intervals, standard errors and p-values are all based on non-parametric
14 10 bootstrapping to increase the robustness of our findings. The data were analysed in SPSS
15 11 (version 22) and Stata (version 13.1).
16
17
18
19
20

21 **Sensitivity analysis**

22 14 The main analysis (using the overarching societal perspective and based on EM imputation)
23 15 was repeated three times in a series of sensitivity analyses. Firstly, the analysis was conducted
24 16 again, but now based on regression imputation (RI) to assess the robustness of the findings
25 17 under a different imputation technique. Secondly, we crosschecked the self-reported
26 18 absenteeism against administrative data derived from the registers of the occupational health
27 19 service or the employer, because the main analysis was based on self-reports and some recall
28 20 bias (underreporting) could have occurred. Finally, we recalculated the incremental net-
29 21 benefits after trimming the highest 5% of total cumulative costs per employee, because the
30 22 participants with the extremely high costs were only a small minority but may have exercised
31 23 a disproportional influence on the cost estimates and pushed outcomes to a more favourable
32 24 outcomes for the ECO intervention. By excluding these participants, primarily from the CAU
33 25 condition, the net-benefits were re-estimated but now under conservative assumptions.
34
35
36
37
38
39
40

41 **RESULTS**

42 43 44 29 **Sample characteristics and baseline costs**

45 30 Baseline characteristics of the sample (including baseline costs) are presented in table 1. The
46 31 mean age of the 220 participants was 44 years and 59% was women. No important differences
47 32 were observed at baseline in demographic characteristics and quality of life, but baseline costs
48 33 were somewhat higher in the ECO condition, suggesting that the ECO group had a slightly
49 34 disadvantageous start. We will return to this issue in the Discussion. As described by Volker
50 35 and colleagues,[22] job characteristics and sickness absence duration at baseline were also
51 36 comparable between the intervention condition and control condition, indicating that the
52 37 randomisation was generally well balanced.
53
54
55
56
57
58
59
60

1 Table 1. Baseline characteristics in the care as usual (CAU) and the ECO intervention group

| | CAU (n=89) | ECO (n=131) |
|--|--------------|--------------|
| Age, mean (SD) | 45.5 (10.7) | 43.3 (9.5) |
| Female, N (%) | 53 (59.6) | 77 (58.8) |
| Married/living together, N (%) | 62 (69.7) | 91 (69.5) |
| Educational level, N (%) | | |
| Low | 32 (36.0) | 48 (36.6) |
| Average | 31 (34.8) | 47 (35.9) |
| High | 26 (29.2) | 36 (27.5) |
| Country of birth: The Netherlands, N (%) | 83 (93.3) | 123 (93.9) |
| Direct medical costs, mean (SD) | 645 (58) | 602 (49) |
| Direct non-medical costs, mean (SD) | 35 (2) | 33 (2) |
| Absenteeism, mean (SD) | 2850 (146) | 3078 (125) |
| Presenteeism, mean (SD) | 34 (16) | 20 (14) |
| Costs in the domestic realm, mean (SD) | 143 (26) | 133 (20) |
| Medication, mean (SD) | 8 (2) | 12 (3) |
| Total costs, mean (SD) | 3716 (154) | 3879 (141) |
| Quality of life, mean (SD) | 0.57 (0.027) | 0.54 (0.024) |

2 **Loss to follow-up**

3 The measurements at 3, 6, 9 and 12 months were completed by 155 (70.5%), 157 (71.4%),
4 134 (60.9%) and 128 (58.2%) of the participants. The dropout rate over the 12-month trial
5 period was higher in the ECO condition (45.0%) than the control condition (37.1%), but this
6 difference was not statistically significant ($\chi^2=1.38$; $df=1$; $p=0.240$). As indicated, we looked
7 for variables that predict dropout and included these as predictors in the EM and IR
8 imputations. This was done to counter selection-bias (if any) and to better meet the MAR
9 assumption underpinning the imputation strategies.

10
11
12 On the topic of treatment adherence, 90 of the 131 participants in the ECO condition (69%)
13 finished the introduction and started with the intervention. These participants had a mean-
14 number of total log-ins of 7.8. Forty percent (36/90) completed at least half of the
15 modules.[22]

16 **Costs and QALYs at 3, 6, 9 and 12 months**

17 The next step of the cost benefit analyses was to ascertain costs and quality of life at the
18 follow-up measurements (Table 2). Cost differences were highest for absenteeism. At 12
19 months all the cost differences were statistically significant and in favour of the ECO condition.
20

1 The total costs difference at the 12 month follow-up amounted to €919 (SE=205; z=4.48;
2 p<0.001), mainly due to reduced absenteeism.

3
4 Table 2. Average monthly costs in the care as usual (CAU) and the ECO intervention group at
5 3, 6, 9 and months (in 2011 Euro)^{1, 2}

| | 3 months | 6 months | 9 months | 12 months |
|----------------------------------|----------|----------|----------|-----------|
| Direct medical costs | | | | |
| CAU | 474 | 298 | 383 | 296 |
| ECO | 460 | 473 | 311 | 144 |
| Cost difference | 14 | -175 | 71 | 153 |
| Direct non-medical costs | | | | |
| CAU | 135 | 74 | 102 | 98 |
| ECO | 104 | 89 | 67 | 45 |
| Cost difference | 31 | -15 | 35 | 53 |
| Productivity losses | | | | |
| Absenteeism | | | | |
| CAU | 2120 | 1699 | 1276 | 1118 |
| ECO | 1887 | 1264 | 725 | 572 |
| Cost difference | 233 | 435 | 551 | 546 |
| Presenteeism | | | | |
| CAU | 166 | 233 | 269 | 493 |
| ECO | 357 | 408 | 322 | 325 |
| Cost difference | -191 | -175 | -53 | 168 |
| Total costs | | | | |
| CAU | 2895 | 2305 | 2029 | 2005 |
| ECO | 2808 | 2234 | 1425 | 1085 |
| Cost difference | 87 | 70 | 605 | 919 |
| Quality of life (utility) | | | | |
| CAU | 0.65 | 0.68 | 0.68 | 0.73 |
| ECO | 0.65 | 0.72 | 0.76 | 0.77 |
| Difference in utilities | 0 | 0.04 | 0.08 | 0.04 |

6
7 1 Between-group differences in italics are statistically significant at p<0.05.

8 2 Numbers may not add due to rounding

1 **Cost-benefit analysis: employer's perspective**

2 For the employer's perspective only the intervention costs and costs stemming from
 3 absenteeism and presenteeism were included, thus assuming that the employer would be
 4 interested to know the pay out of this investment when paying for the intervention. Cumulated
 5 over the 12-months period the incremental benefits were €3,487 in favour of the ECO
 6 condition (Bootstrapped 95% CI= -418~7,390; SE=1,992; z=1.75; p=0.080), which was
 7 mainly due to a larger reduction in absenteeism over 12 months compared to care as usual
 8 (bootstrapped M=4,291; 95% CI= 290~8,292; SE=2,041; z=2.10; p=0.036). Next, we
 9 calculated incremental net-benefits, by subtracting the intervention costs (€300) from the
 10 incremental benefits. As shown in table 3 the incremental net-benefits over twelve months
 11 were €3,187 per employee in favour of the ECO condition, but there is significant uncertainty
 12 in the estimate (Bootstrapped 95% CI=-656~7,029; SE=1,961; z=1.63; p=0.104). We return
 13 to this issue in the Discussion. The break-even point for the employer, the moment in time
 14 where the investment of €300 is recouped, is around six months. The return of investment
 15 (ROI) is $3,187/300=10.62$, indicating that for every euro invested the pay-out is €10.6.

16
 17 Table 3. Monthly per patient costs in the care as usual (CAU) and the ECO intervention group
 18 from an employer's perspective (in 2011 Euro)

| Month | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Cumulative |
|--------------------------|------|------|------|------|------|------|------|------|------|------|------|------|------------|
| CAU | | | | | | | | | | | | | |
| Absenteeism | 2850 | 2485 | 2120 | 1910 | 1910 | 1699 | 1487 | 1487 | 1276 | 1197 | 1197 | 1118 | 20736 |
| Presenteeism | 34 | 100 | 166 | 199 | 199 | 233 | 251 | 251 | 269 | 380 | 380 | 493 | 2955 |
| Total costs | 2884 | 2585 | 2286 | 2109 | 2109 | 1932 | 1738 | 1738 | 1545 | 1577 | 1577 | 1611 | 23691 |
| ECO | | | | | | | | | | | | | |
| Absenteeism | 3078 | 2483 | 1887 | 1576 | 1576 | 1264 | 994 | 994 | 725 | 648 | 648 | 572 | 16445 |
| Presenteeism | 20 | 188 | 357 | 382 | 382 | 408 | 365 | 365 | 322 | 323 | 323 | 325 | 3760 |
| Total costs | 3098 | 2671 | 2244 | 1958 | 1958 | 1672 | 1359 | 1359 | 1047 | 971 | 971 | 897 | 20205 |
| Incremental benefits | -214 | -86 | 42 | 151 | 151 | 260 | 379 | 379 | 498 | 606 | 606 | 714 | 3486 |
| Intervention costs | -300 | | | | | | | | | | | | |
| Incremental net-benefits | -514 | -600 | -558 | -407 | -256 | 4 | 383 | 762 | 1260 | 1866 | 2472 | 3186 | |
| Return on investment | 10.6 | | | | | | | | | | | | |

19

20 **Cost-benefit analysis: health care payer's perspective**

21 For the perspective of the health care financier we looked at the direct medical costs including
 22 the costs for medication. We computed the monthly cash flows and compared these between
 23 the ECO and CAU conditions as before. The cumulative costs over twelve months were more or
 24 less the same for each condition with a small difference of €87 in favour of the ECO condition.
 25 Assuming that the health insurer would pay for the intervention, the intervention costs of €300

1
2
3 1 have to be subtracted from these benefits in order to obtain the net-benefits. This generated a
4 2 negative value of €213, implying that the ECO intervention is not cost saving from a health
5 3 care insurer's perspective (bootstrapped 95% CI=-1,384~959; SE=598; z=-0.36; p=0.722).
6 4

5 **Cost-benefit analysis: employee's perspective**

6 Employee's costs and benefits included direct non-medical costs (i.e. the patient's out-of-
7 pocket costs and costs in the domestic realm) and QALY health gains. Cumulated over twelve
8 months the incremental benefits for the ECO group were €263 regarding non-medical costs
9 and €696 due to QALY gains (0.035*€20,000). The incremental net-benefits were €959-€300=
10 659 (bootstrapped 95% CI=287~1,031; SE=190; z=3.47; p=0.001). The break-even point
11 occurred at eight months and the return on investment was 659/300=2.2.
12

13 **Cost-benefit analysis: societal perspective**

14 For the societal perspective we included the costs and benefits of all stakeholders. The
15 difference between conditions of the cumulative benefits was €29,823-€25,290=€4,533 in
16 favour of the intervention condition (bootstrapped 95% CI= 141~8,925; SE=2,241; z=2.02
17 p=0.043). Subtraction of the intervention costs of €300 yielded incremental net-benefits from
18 a social perspective of €4,233 (bootstrapped 95% CI= -194~8,660; SE=2,259; z=1.87;
19 p=0.061). Break-even was achieved at seven months and the return on investment was
20 4,233/300= 14.1.
21

22 **Sensitivity analyses**

23 For the main analysis we used EM imputation; now we recomputed the estimates under
24 regression imputation (RI). Taking the societal perspective, the incremental net-benefits
25 became €4,093 (Bootstrapped 95% CI= -279~8,465; SE=2,231; z=1.83; p=0.067) and the
26 return on investment 4,093/300=13.6, which is close to the EM-based analysis (see table 4).
27

28 The incremental net-benefits in the main analyses were dominated by the costs offsets due to
29 reduced absenteeism, but these were based on self-reported data. Crosschecking the self-
30 reported data against administrative data derived from the registers of the occupational health
31 service or employer showed that the estimates for days absent were lower in the analysis
32 based on self-report data than on administrative data (72 work days absent based on self-
33 reported data versus an average of 101 work days absent based on administrative data).
34 When basing the analysis on administrative data, the total cumulative incremental net-benefits
35 became €6,154 (Bootstrapped 95% CI=-3,352~15,660; SE=4,850; z=1.27; p=0.205), which
36 is higher by a factor 1.5 than the corresponding estimate presented in the main analysis. The
37 main analysis thus represents a safer (lower) estimate.
38

1
2
3 1 Finally, we repeated the main analysis by replacing the total costs of the respondents with the
4 2 top 5% highest total costs due to absenteeism by the highest amount witnessed in the other
5 3 95% respondents. The top 5% outliers were mainly situated in the CAU condition, raising the
6 4 average costs for this group. The incremental net-benefits based on the trimmed costs
7 5 dropped from €4,233 to €3,613 (SE 95% CI= -491~7,718; SE=2,094; z=1.73; p=0.084),
8 6 which can be regarded as a more conservative lower bound.
9 7

8 Table 4. Incremental net-benefit and return on investment from societal perspective for base
9 case and sensitivity analyses (in 2011 Euro)

| | Incremental net-benefit | Return on investment |
|---|-----------------------------|----------------------|
| Base case analysis | 4,233 (-194 to 8,660) | 14.1 |
| sensitivity analysis regression imputation | 4,093 (-279 to 8,465) | 13.6 |
| sensitivity analysis administrative data | 6,154 (-3,352 to 15,660) | 20.5 |
| sensitivity analysis trimming highest 5% | 3,613 (-491 to 7,718) | 12.0 |

11 DISCUSSION

13 Principal findings

14 This study was set out to evaluate the cost-effectiveness of an intervention that encourages
15 sick-listed employees with (symptoms of) common mental disorders to make an early return to
16 their work. The economic evaluation was conducted as an incremental cost-benefit analysis
17 and reports on the incremental cost to benefit ratio, the return on investment, the break-even
18 point, and the incremental monetary net-benefits, as customary seen in business cases and
19 investment appraisals. These metrics were computed from various perspectives: the
20 perspective of the employer, the employee, the health care financier and society. The main
21 findings can now be summarised as follows:

- 22 • Taking the employer's perspective, the focus of the economic evaluation was placed on the
23 intervention costs and changes in productivity owing to changes in absenteeism and
24 presenteeism. Assuming that the employer would make the investment in the ECO
25 intervention of €300 per employee, the incremental net-benefits were €3,187 per employee
26 over a year. This was equivalent to a return on investment of €11 per invested Euro.
27 Benefits largely stemmed from reduced absenteeism and exceeded the investment costs
28 after six months.
- 29 • From the perspective of the health care payer the incremental net-benefits were negative,
30 amounting to additional costs of €213 per employee on average.

- 1 • As seen from the employee the net-benefits exceeded the costs by €659 when also valuing
2 the employee's QALY health gains. When excluding the QALY benefits, the incremental net-
3 benefits were slightly negative (€37).
- 4 • From the societal perspective, the initial investment was also more than recouped.
5 Considering all costs and benefits, but ignoring the value of QALY gains, the incremental
6 net-benefits were €4,233, with a break-even point at 7 months. Every euro invested
7 yielded €14. Trimming the 5% highest costs, mostly from the care as usual condition,
8 reduced the incremental net-benefits to €3,613.

10 **Limitations**

11 This study has several limitations, which are reported and discussed here.

- 12 • First, cost data are often non-normally distributed with a some people generating very high
13 costs. This results in large standard deviations in the costs estimates and less precise
14 estimates of average costs. In such a context it would require a very large sample size to
15 power the trial for testing economic hypotheses. However, our study was only powered to
16 test a difference in sickness absence duration. As a consequence, the wide 95% confidence
17 intervals indicate that the cost estimates are subject to much uncertainty. More specifically,
18 when trimming the highest 5% of the costs in one of our sensitivity analysis showed that
19 the incremental net-benefits became €3,613, which is 85% of the original estimate of
20 €4,233. This suggests that our study needs replication, preferably in a larger study.
- 21 • Second, loss-to follow up was substantial. To handle dropout, missing data were imputed
22 using estimation maximization (EM). To ascertain the robustness of our findings we also
23 used regression imputation (RI). With RI we arrived at similar conclusions: €4,093 (versus
24 €4,233 under EM), attesting to the robustness in our findings. Nonetheless, selection bias
25 introduced by (selective) dropout cannot be ruled out completely and could have influenced
26 the outcomes that we obtained.
- 27 • Third, costs at baseline were higher in the ECO condition. We could have adjusted for the
28 baseline differences, but this would have led to even better outcomes in favour of the ECO
29 condition. Ignoring the baseline differences has therefore put our main analyses on a more
30 conservative footing.
- 31 • Fourth, the main driver of costs and benefits was absenteeism and in the main analysis
32 these were based on self-report. This may have introduced some recall bias, but self-
33 reports of absenteeism usually involve underreporting thus leading to conservative
34 outcomes. Still, we crosschecked the self-reports against administrative data from the
35 registers of the occupational health service and the employer. As expected, the benefits
36 were lower when based on self-reports than on administrative data.
- 37 • Fifth, it should be noted that the cost-benefit analysis did not include the future costs of
38 implementing the ECO intervention on a wider scale. As the main component is a low cost

- 1
2
3 1 self-help intervention (Return@Work) and the training of OPs only lasts a few hours, the
4 2 implementation costs are expected to be low, but should be considered when the
5 3 intervention is disseminated on a wider scale.
6
7 4 • Finally, the follow-up time is limited to 12 months. We do not know what the net-benefits
8 5 would be over a longer time span. However, costs differences were highest in the last
9 6 months. This may imply that a longer follow-up period would have seen more profitable
10 7 outcomes.
11
12
13 8

14 9 **Results in context**

15
16 10 Reviews about the effectiveness of psychological return to work interventions for employees
17 11 with mental health problems show mixed outcomes in reducing sickness absence and
18 12 promoting an earlier return to work.[12, 23] Moreover, only a few of the reviewed studies that
19 13 appeared to be effective report a full economic evaluation. Of these, none evaluated a guided
20 14 eHealth intervention for return to work. One study that is somewhat comparable with our
21 15 study is from Schene and colleagues. Schene et al describe the economic evaluation of an
22 16 intervention for employees with major depression, who were sick-listed between 10 weeks and
23 17 2 years.[41] The experimental condition received occupational therapy in addition to usual
24 18 outpatient treatment for depression. Their intervention increased the number of hours worked
25 19 accumulating in a median economic gain of US\$4000–5000 per patient per year, which is in
26 20 line with our findings regarding the reduction in absenteeism. The study of Schene et al was
27 21 smaller (n=62), was directed at a more severely depressed population, and the intervention
28 22 was not delivered online but as an intensive face-to-face therapy consisting of 24 group
29 23 sessions and 15 individual sessions.
30
31
32
33
34
35
36
37 24

38 25 Lerner and colleagues evaluated a brief telephonic program to improve work functioning for
39 26 employees with major depressive disorder or dysthymia with an at-work productivity loss of at
40 27 least 5% in the past two weeks.[42] Compared to usual care, annualised cost savings
41 28 averaged at \$6042 per participant but these savings were extrapolated from a shorter (4
42 29 months) follow-up. These cost savings are higher than the cost-savings observed in our study.
43
44
45 30 Nonetheless, Lerner's et al. extrapolation from 4 to 12 months might have overstated the
46 31 savings if the treatment effect was not sustained.
47
48
49
50
51
52
53
54
55
56
57
58
59
60

33 Arends and colleagues evaluated the costs and benefits of a problem-solving intervention
34 34 provided by OPs to prevent recurrent sickness absence in workers with common mental
35 35 disorders.[43] Compared to care as usual the intervention was more effective but also more
36 36 expensive. From an employer's perspective the intervention showed no economic benefits,
37 37 which is in contrast to our study.
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 1 Noben and colleagues conducted a cost-benefit analysis from the employer's perspective of a
4 2 preventive intervention in the work setting among nurses with an elevated-risk of mental
5 3 complaints.[44] The authors concluded that the intervention was a good investment as the
6 4 net-benefits (stemming from reduced absenteeism and presenteeism) were positive (€651)
7 5 and the return on investment was €11 per Euro spent. This return on investment is
8 6 comparable with ours.
9 7

10 8 In contrast to Noben and colleagues and several other studies [45] we found negative results
11 9 for presenteeism in the short run (first nine months), but these were alleviated in the longer
12 10 run (at the end of the year). An explanation for the initially negative results on presenteeism
13 11 might be that employees who returned to work early were not completely fit and as productive
14 12 as normally. In other words there was an initial trade-off between reduced absenteeism and
15 13 increased presenteeism. However, after the first nine months the additional costs caused by
16 14 presenteeism ceased to exist and were reversed into benefits. This change is possibly driven
17 15 by an improvement in quality of life when people work.
18 16

19 17 The literature suggests that in terms of economic costs presenteeism often is a larger problem
20 18 than absenteeism. Our results are not in line with these findings. This could be due to the
21 19 Dutch system in which employees receive a substantial percentage of their wage during the
22 20 first two years of their illness. In many other countries the fall in income is more acute when
23 21 employees stay absent from their work, increasing the incentive to keep on working – even
24 22 when work is then associated with greater levels of presenteeism.
25 23

26 24 The results of our study can only be generalised to employees who have been sick-listed for 4-
27 25 26 weeks, working in small- to medium-sized companies.
28 26

27 **Conclusions and implications**

28 28 In the Netherlands, employers have an incentive to invest in sickness management as they
29 29 have the responsibility to pay 70-100% of the salary of sick-listed employees for up to two
30 30 years. Employees who are on sickness absence have to visit an occupational physician, paid by
31 31 the employer within the first six weeks. Both the employee and employer have to agree on an
32 32 action plan. In this plan the responsibilities of both parties are defined to ensure a quick return
33 33 to work of the employee. In this context the ECO-intervention can be seen as an effective
34 34 intervention that, in addition, has a high probability of offering good value for money because
35 35 the initial investment (of €300) is more than recouped within a single year as seen from the
36 36 employer's perspective, while the employee derives benefits in the form of increased quality of
37 37 life when returning to work sooner rather than later. As noted, some 95% confidence intervals
38 38 of our estimates are wide. By implication, one should not rely too much on the point estimates
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 1 of net-benefits, return on investment ratios, break-even points, because they lack precision. In
4 2 other words, our estimates, although conservative, have some degree of uncertainty and are
5 3 therefore no substitute for one's own business judgement.
6
7 4

5 **Acknowledgements**

6 We acknowledge with many thanks Prof.dr. H Anema (VU University) for advice on the design
7 of the study, Dr. G. van Lomwel (ACHMEA/UWV) for advice on design of the study and
8 providing access to data, and Dr. M. Blankers for help with statistical analyses.
9

10 **Contributors**

11 CFC initiated the collaborative clinical trial project. MZV, AB and CFC contributed to the design
12 of the study and obtained the funding. DV, MZV and CFC were responsible for the acquisition
13 of the data. SL and FS conducted the statistical analysis and drafted the manuscript, which all
14 authors critically revised. All authors read and approved the final manuscript. SL, FS and CFC
15 are guarantors.
16

17 **Funding**

18 This study was financially supported by The Netherlands Organization for Health Research and
19 Development (ZonMw) (grant number 171002403) and Achmea, a Dutch health insurance
20 company. The funding sources had no role in the data analysis and interpretation and in the
21 writing of this paper.
22

23 **Competing interests**

24 All authors have completed the ICMJE uniform disclosure form at
25 www.icmje.org/coi_disclosure.pdf and declare: financial support for the submitted work from
26 The Netherlands Organisation for Health Research and Development (ZonMw) and from
27 Achmea SZ; SL, DV, MZV, BB, FS report personal fees from employment at the Trimbos
28 institute, the Netherlands institute of mental health and addiction, a not-for-profit
29 organisation, CFC has received research grants from Eli Lilly outside the submitted work.
30

31 **Ethical approval**

32 The study protocol was approved by the Medical Ethics Committee of the University Medical
33 Center Utrecht, The Netherlands, in February 2011. All participants provided written informed
34 consent before taking part.
35

36 **Transparency**

1
2
3 1 The lead author affirms that the manuscript is an honest, accurate and transparent account of
4 2 the study being reported; that no important aspects of the study have been omitted; and that
5 3 and discrepancies from the study as planned (and if relevant, registered) have been explained.
6 4

7
8
9 5 Data sharing: No additional data
10 6

11 7 **Copyright**

12 8 The Corresponding Author has the right to grant on behalf of all authors and does grant on
13 9 behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all
14 10 forms, formats and media (whether known now or created in the future), to i) publish,
15 11 reproduce, distribute, display and store the Contribution, ii) translate the Contribution into
16 12 other languages, create adaptations, reprints, include within collections and create summaries,
17 13 extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on
18 14 the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of
19 15 electronic links from the Contribution to third party material where-ever it may be located;
20 16 and, vi) licence any third party to do any or all of the above.
21 17

22 18 **Legends of figures**

23 19 Figure 1. Flowchart of the clusters and participants
24 20

25 21 **References**

- 26 22 1. Lerner D, Amick BC, Lee JC, et al. Relationship of employee-reported work limitations to
27 23 work productivity. *Med Care* 2003;41(5):649–59. doi:10.1097/01.MLR.0000062551.76504.A9.
28 24
- 29 25 2. Adler DA, McLaughlin TJ, Rogers WH, et al. Job performance deficits due to depression. *Am*
30 26 *J Psychiatry* 2006 Sep;163(9):1569–76. doi:10.1176/ajp.2006.163.9.1569.
31 27
- 32 28 3. Moncrieff J, Pomerleau J. Trends in sickness benefits in Great Britain and the contribution of
33 29 mental disorders. *J Public Health Med* 2000;22(1):59-67. doi:10.1093/pubmed/22.1.59.
34 30
- 35 31 4. Shiels C, Gabbay MB, Ford FM. Patient factors associated with duration of certified sickness
36 32 absence and transition to long-term incapacity. *Br J Gen Pract* 2004;54(499):86-91.
37 33
- 38 34 5. Cattrell A, Harris EC, Palmer KT, et al. Regional trends in awards of incapacity benefit by
39 35 cause. *Occup Med (Lond)* 2011;61(3): 148-151. doi:10.1093/occmed/kqr008 [published
40 36 Online First: 11 April 2011].
41 37
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 6. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases
4 2 and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease
5 3 Study 2010. *Lancet* 2012;380:2197-2223. doi:10.1016/S0140-6736(12)61689-4 [published
6 4 Online First: 22 February 2013].
7
8 5
9
10 6 7. de Graaf R, Tuithof M, van Dorsselaer S, et al. Sick leave due to psychological and physical
11 7 illnesses among employees: results of the 'Netherlands Mental Health Survey and Incidence
12 8 Study-2' (NEMESIS-2) [in Dutch: Verzuim door psychische en somatisch aandoeningen bij
13 9 werkenden: resultaten van de 'Netherlands Mental Health Survey and Incidence Study-2'
14 10 (NEMESIS-2)]. Utrecht: Trimbos-instituut 2011.
15 11
16 12 8. Lelliott P, Tulloch S, Boardman J, et al. Mental Health and Work. London: Cross Government
17 13 Health Work and Well-being Programme 2008.
18 14
19 15 9. Chisholm D, Sanderson K, Ayuso-Mateos JL, et al. Reducing the global burden of
20 16 depression. *Br J Psychiatry* 2004;184:393-403. doi:10.1192/bjp.184.5.393.
21 17
22 18 10. Harvey SB, Joyce S, Modini M, et al. Work and depression/anxiety disorders: a systematic
23 19 review of reviews. Melbourne, Australia: Beyondblue 2013.
24 20
25 21 11. Ejeby K, Savitskij R, Ost LG, et al. Symptom reduction due to psychosocial interventions is
26 22 not accompanied by a reduction in sick leave: results from a randomized controlled trial in
27 23 primary care. *Scand J Prim Health Care* 2014;32(2):67-72.
28 24 doi:10.3109/02813432.2014.909163 [published Online First: 17 April 2014].
29 25
30 26 12. Nieuwenhuijsen K, Faber B, Verbeek JH, et al. Interventions to improve return to work in
31 27 depressed people. *Cochrane Database Syst Rev* 2014;12:CD006237.
32 28 doi:10.1002/14651858.CD006237 [published Online First: 3 December 2014].
33 29
34 30 13. OECD (2014). Mental Health and Work: Netherlands, Mental Health and Work. Paris: OECD
35 31 Publishing. doi:10.1787/9789264223301-en.
36 32
37 33 14. Willems JHBM, Doppegieter RMS. De scheiding van 'behandeling en controle': aan
38 34 actualisering toe? *Tijdschrift voor Bedrijfs- en Verzekeringsgeneeskunde* 2007;15(4):164-
39 35 167. doi:10.1007/BF03074555.
40 36
41 37
42 38
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 15. van der Klink JJL. Richtlijn: Handelen van de bedrijfsarts bij werkenden met psychische
4 2 problemen. [Guideline: The management of mental health problems of workers by
5 3 occupational physicians] Eindhoven: NVAB [Netherlands Society of Occupational Medicine]
6 4 2000.
7 5
8
9
10 6 16. Rebergen DS, Bruinvels DJ, Bos CM, et al. Return to work and occupational physicians'
11 7 management of common mental health problems – process evaluation of a randomized
12 8 controlled trial. *Scand J Work Environ Health* 2010;36(6):488-498. doi:10.5271/sjweh.3084.
13 9
14
15
16 10 17. Rebergen D, Hoenen J, Heinemans A, et al. Adherence to mental health guidelines by
17 11 Dutch occupational physicians. *Occup Med (Lond)* 2006;56(7):461-468.
18 12 doi:10.1093/occmed/kql042 [published Online First: 16 June 2006].
19 13
20
21
22 14 18. Rebergen DS, Bruinvels DJ, Bezemer PD, et al. Guideline-based care of common mental
23 15 disorders by occupational physicians (CO-OP study): a randomized controlled trial. *J Occup
24 16 Environ Med* 2009;51(3):305-312. doi:10.1097/JOM.0b013e3181990d32.
25 17
26
27
28 18 19. Van der Feltz CM, Hoedeman R, de Jong FJ, et al. Faster return to work after psychiatric
29 19 consultation for sicklisted employees with common mental disorders compared to care as
30 20 usual. A randomized clinical trial. *Neuropsychiatr Dis Treat*. 2010;6:375–385. [published
31 21 Online First: 2 July 2010].
32 22
33
34
35 23 20. Vlasveld MC, van der Feltz-Cornelis CM, Adèr HJ, et al. Collaborative care for sick-listed
36 24 workers with major depressive disorder: a randomised controlled trial from the Netherlands
37 25 Depression Initiative aimed at return to work and depressive symptoms. *Occup Environ Med*
38 26 2013;70(4):223-230. doi:10.1136/oemed-2012-100793 [published Online First: 29 October
39 27 2012].
40
41
42
43
44 29 21. Volker D, Vlasveld MC, Anema JR, et al. Blended E-health module on return to work
45 30 embedded in collaborative occupational health care for common mental disorders: design of a
46 31 cluster randomized controlled trial. *Neuropsychiatr Dis Treat* 2013;9:529-537.
47 32 doi:10.2147/NDT.S43969 [published Online First: 19 April 2013].
48 33
49
50
51 34 22. Volker D, Zijlstra-Vlasveld MC, Anema JR, et al. Effectiveness of a Blended Web-Based
52 35 Intervention on Return to work for Sick-Listed Employees With Common Mental Disorders:
53 36 Results of a Cluster Randomized Controlled Trial. *J Med Internet Res* 2015;17(5):e116.
54 37 doi:10.2196/jmir.4097 [published Online First: 13 May 2015].
55 38
56
57
58
59
60

- 1
2
3 1 23. Arends I, Bruinvels DJ, Rebergen DS, et al. Interventions to facilitate return to work in
4 2 adults with adjustment disorders. *Cochrane database Syst Rev*. 2012;12:CD006389.
5 3 doi:10.1002/14651858.CD006389.pub2 [published Online First: 12 December 2012].
6 4
7 4
8 5 24. Henderson M, Glozier N, Holland EK. Long term sickness absence. *BMJ*. 2005;330:802–
9 6 803. doi: <https://doi.org/10.1136/bmj.330.7495.802> [published Online First: 07 April 2005].
10 7
11 7
12 8 25. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity
13 9 measure. *J Gen Intern Med* 2001;16(9):606-613.
14 10 doi:10.1046/j.1525-1497.2001.016009606.x [published Online First: 20 December 2001].
15 11
16 12 26. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: validity of a new measure for
17 13 evaluating the severity of somatic symptoms. *Psychosom Med* 2002;64(2):258-266.
18 14 doi:10.1097/00006842-200203000-00008.
19 15
20 16 27. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized
21 17 anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166(10):1092-1097.
22 18 doi:10.1001/archinte.166.10.1092.
23 19
24 20 28. Nieuwenhuijsen K, Noordik E, van Dijk FJH, et al. Return to work perceptions and actual
25 21 return to work in workers with common mental disorders. *J Occup Rehabil*. 2013;23(2):290–9.
26 22 doi:10.1007/s10926-012-9389-6 [published Online First: 3 November 2012].
27 23
28 24 29. van Oostrom SH, Mechelen van MW, Terluin B, et al. A workplace intervention for sick-
29 25 listed employees with distress: results of a randomised controlled trial. *Occup*
30 26 *Environ Med* 2010;67(9):596–602. doi:10.1136/oem.2009.050849 [published Online First: 2
31 27 April 2010].
32 28
33 29 30. Volker D, Zijlstra-Vlasveld MC, Brouwers EPM, et al. Return-to-work self-efficacy and
34 30 actual return to work among long-term sick-listed employees. *J Occup Rehabil* 2015; 25
35 31 (2):423-341. doi:10.1007/s10926-014-9552-3 [published Online First: 30 October 2014].
36 32
37 33 31. Hakkaart-van Roijen L. Manual Trimbos/iMTA questionnaire for costs associated with
38 34 psychiatric illness (in Dutch). Rotterdam: Institute for Medical Technology Assessment 2002.
39 35
40 36 32. Euroqol Group. *Eq-5D User Guide*. Rotterdam, The Netherlands: Sanders Instituut, EUR
41 37 1995.
42 38
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 33. Lamers, L. M., McDonnell, J., Stalmeier, P. F. M., Krabbe, P. F. M., & Busschbach, J. J. V.
4 2 (2006). The Dutch tariff: results and arguments for an effective design for national EQ-5D
5 3 valuation studies. *Health Econ*, 15(10), 1121-32. doi:10.1002/hec.1124 [published Online
6 4 First: 19 June 2006].
7
8 5
9
10 6 34. Hakkaart L, Tan S, Bouwmans C. Manual for cost research. Methods and standard costs for
11 7 economic evaluations in healthcare (in Dutch). Rotterdam: Institute for Medical Technology
12 8 Assessment, Erasmus University Rotterdam 2010.
13 9
14
15
16 10 35. Zorginstituut Nederland (2014a). Dutch Health Care Insurance Board (in Dutch)
17 11 (<http://www.medicijnkosten.nl/>). Accessed 7 May 2014.
18 12
19
20 13 36. Zwaap J, Knies S, van der Meijden C, et al. Kosteneffectiviteit in de praktijk. Diemen:
21 14 Zorginstituut Nederland 2015.
22 15
23
24
25 16 37. Rice DP, Cooper BS. The economic value of human life. *Am J Public Health Nations Health*
26 17 1967;57:1954–1966. doi: 10.2105/AJPH.57.11.1954.
27 18
28
29 19 38. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for
30 20 reporting parallel group randomised trials. *BMJ* 2010;340:c332. doi:10.1136/bmj.c332.
31 21
32
33 22 39. Campbell MK, Piaggio G, Elbourne DR, et al. Consort 2010 statement: extension to cluster
34 23 randomised trials. *BMJ* 2012;345:e5661. doi:10.1136/bmj.e5661.
35 24
36
37
38 25 40. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation
39 26 Reporting Standards (CHEERS) statement. *BJOG* 2013;120:765-770. doi:10.1136/bmj.f1049.
40 27
41
42 28 41. Schene AH, Koeter MW, Kikkert MJ, et al. Adjuvant occupational therapy for work-related
43 29 major depression works: randomized trial including economic evaluation. *Psychol*
44 30 *Med* 2007;37:351–362. doi:dx.doi.org/10.1017/S0033291706009366 [published Online First:
45 31 20 November 2006].
46 32
47
48
49
50 33 42. Lerner D, Adler D, Hermann RC, et al: Impact of a work-focused intervention on the
51 34 productivity and symptoms of employees with depression. *J Occup Environ Med* 54:128–135,
52 35 2012. doi:10.1097/JOM.0b013e31824409d8 [published Online First: 1 March 2015].
53 36
54
55
56 37 43. Arends I, Bültmann U, van Rhenen W, et al. Economic evaluation of a problem solving
57 38 intervention to prevent recurrent sickness absence in workers with common mental disorders.
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

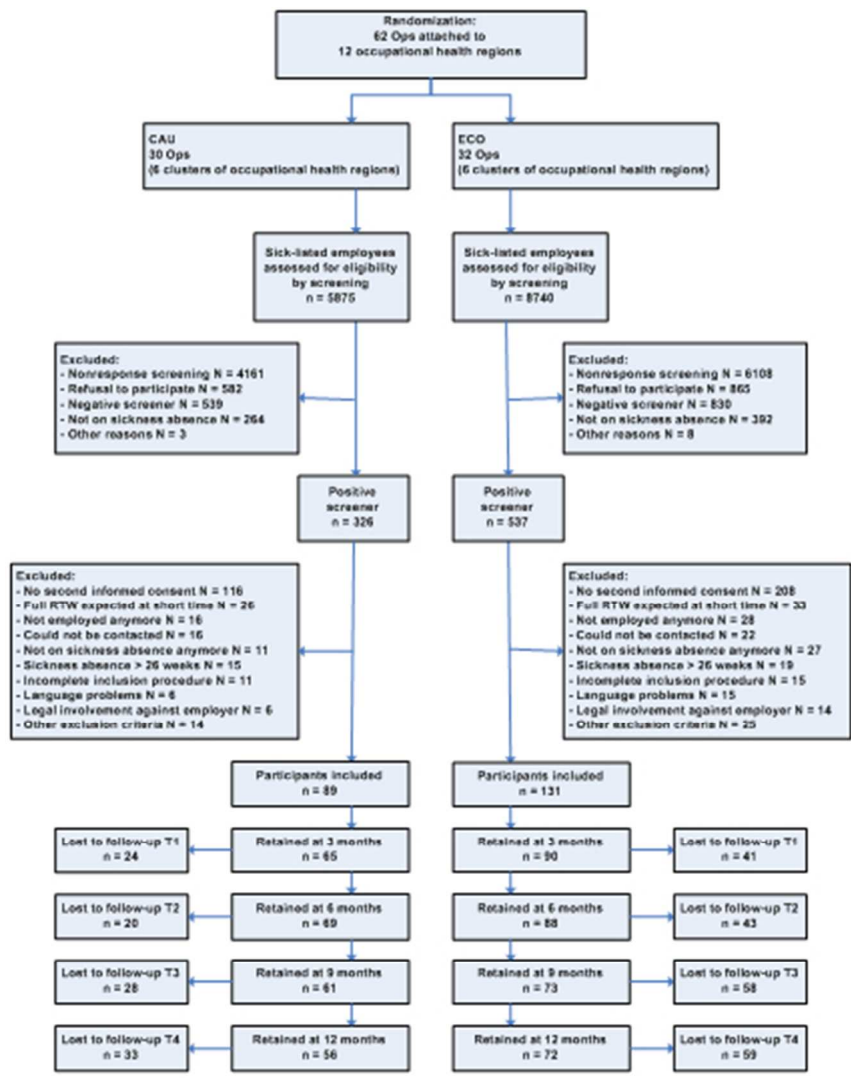
1 *PLoS One* 2013;8:e71937. doi:10.1371/journal.pone.0071937 [published Online First: 12
2 August 2013].

3
4
5
6
7
8 44. Noben C, Evers S, Nieuwenhuijsen K, et al. Protecting and promoting mental health of
9 nurses in the hospital setting: is it cost-effective form an employer’s perspective?
10 *Int J Occup Med Environ Health* 2015;28(5). doi:10.13075/ijomeh.1896.00465.

11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

8 45. Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from
9 disease and injury: disability weights measurement study for the Global Burden of Disease
10 Study 2010. *Lancet*. 2012;380:2129–43. doi:10.1016/S0140-6736(12)61680-8.

For peer review only



Flowchart of the participants



Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

| Section/Topic | Item No | Standard Checklist item | Extension for cluster designs | Page No * |
|----------------------------------|---------|--|---|-----------|
| Title and abstract | | | | |
| | 1a | Identification as a randomised trial in the title | Identification as a cluster randomised trial in the title | 3 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) ^{1,2} | See table 2 | 3 |
| Introduction | | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | Rationale for using a cluster design | 4,5 |
| | 2b | Specific objectives or hypotheses | Whether objectives pertain to the cluster level, the individual participant level or both | 5 |
| Methods | | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | Definition of cluster and description of how the design features apply to the clusters | 5 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | | N/A |
| Participants | 4a | Eligibility criteria for participants | Eligibility criteria for clusters | 6 |
| | 4b | Settings and locations where the data were collected | | 6 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | Whether interventions pertain to the cluster level, the individual participant level or both | 7 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and | Whether outcome measures pertain to the cluster level, the individual participant level or both | 7/8 |

| | | | | |
|---|-----|---|---|-----|
| | | when they were assessed | | |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | | N/A |
| Sample size | 7a | How sample size was determined | Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or <i>k</i>), and an indication of its uncertainty | N/A |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | | N/A |
| Randomisation: | | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | | 6 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | Details of stratification or matching if used | 5/6 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both | 5/6 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | Replace by 10a, 10b and 10c | 6 |
| | 10a | | Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions | |
| | 10b | | Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete | |

| | | | | |
|---|-----|--|---|---------|
| | | | enumeration, random sampling) | |
| | 10c | | From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation | |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | | 6 |
| | 11b | If relevant, description of the similarity of interventions | | N/A |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | How clustering was taken into account | 9/10 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | | 10 |
| Results | | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome | 6/10/11 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | For each group, losses and exclusions for both clusters and individual cluster members | 10/11 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | | 6 |
| | 14b | Why the trial ended or was stopped | | N/A |
| Baseline data | 15 | A table showing baseline demographic and clinical | Baseline characteristics for the individual and cluster levels as | Table 1 |

| | | characteristics for each group | applicable for each group | |
|--------------------------------|-----|---|--|-------|
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | For each group, number of clusters included in each analysis | 6/9 |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome | 11-15 |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | | N/A |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | | 14/15 |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms ³) | | N/A |
| Discussion | | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | | 16/17 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | Generalisability to clusters and/or individual participants (as relevant) | 17 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | | 17-19 |
| Other information | | | | |
| Registration | 23 | Registration number and | | 5/6 |

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

| | | |
|-----------------|----|---|
| | | name of trial registry |
| Protocol | 24 | Where the full trial protocol can be accessed, if available |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders |

** Note: page numbers optional depending on journal requirements*

For peer review only

Table 2: Extension of CONSORT for abstracts^{1,2} to reports of cluster randomised trials

| Item | Standard Checklist item | Extension for cluster trials |
|---------------------------|---|--|
| Title | Identification of study as randomised | Identification of study as cluster randomised |
| Trial design | Description of the trial design (e.g. parallel, cluster, non-inferiority) | |
| Methods | | |
| Participants | Eligibility criteria for participants and the settings where the data were collected | Eligibility criteria for clusters |
| Interventions | Interventions intended for each group | |
| Objective | Specific objective or hypothesis | Whether objective or hypothesis pertains to the cluster level, the individual participant level or both |
| Outcome | Clearly defined primary outcome for this report | Whether the primary outcome pertains to the cluster level, the individual participant level or both |
| Randomization | How participants were allocated to interventions | How clusters were allocated to interventions |
| Blinding (masking) | Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment | |
| Results | | |
| Numbers randomized | Number of participants randomized to each group | Number of clusters randomized to each group |
| Recruitment | Trial status ¹ | |
| Numbers analysed | Number of participants analysed in each group | Number of clusters analysed in each group |
| Outcome | For the primary outcome, a result for each group and the estimated effect size and its precision | Results at the cluster or individual participant level as applicable for each primary outcome |
| Harms | Important adverse events or side effects | |
| Conclusions | General interpretation of the results | |
| Trial registration | Registration number and name of trial register | |
| Funding | Source of funding | |

¹ Relevant to Conference Abstracts

REFERENCES

- 1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283
- 2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20
- 3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

| Section/item | Item No | Recommendation | Reported on page No/line No |
|---------------------------------|---------|--|-----------------------------|
| Title and abstract | | | |
| Title | 1 | Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared. | 3 |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | 3 |
| Introduction | | | |
| Background and objectives | 3 | Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions. | 4,5 |
| Methods | | | |
| Target population and subgroups | 4 | Describe characteristics of the base case population and subgroups analysed, including why they were chosen. | 6 |
| Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | 6 |
| Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | 9 |
| Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen. | 7 |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | 8 |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | 8 |
| Choice of health outcomes | 10 | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed. | 8/9 |
| Measurement of effectiveness | 11a | <i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. | 5-7 |



| | | | | |
|----|-------------------------|-----|---|-------|
| 1 | | 11b | <i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data. | N.A. |
| 2 | | | | |
| 3 | | | | |
| 4 | | | | |
| 5 | Measurement and | 12 | If applicable, describe the population and methods used to elicit preferences for outcomes. | N.A. |
| 6 | valuation of preference | | | |
| 7 | based outcomes | | | |
| 8 | Estimating resources | 13a | <i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | 7,8 |
| 9 | and costs | | | |
| 10 | | 13b | <i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | N.A. |
| 11 | | | | |
| 12 | | | | |
| 13 | | | | |
| 14 | | | | |
| 15 | | | | |
| 16 | | | | |
| 17 | | | | |
| 18 | | | | |
| 19 | | | | |
| 20 | | | | |
| 21 | | | | |
| 22 | | | | |
| 23 | Currency, price date, | 14 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate. | 8 |
| 24 | and conversion | | | |
| 25 | | | | |
| 26 | | | | |
| 27 | | | | |
| 28 | | | | |
| 29 | Choice of model | 15 | Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended. | N.A. |
| 30 | | | | |
| 31 | | | | |
| 32 | Assumptions | 16 | Describe all structural or other assumptions underpinning the decision-analytical model. | N.A. |
| 33 | | | | |
| 34 | Analytical methods | 17 | Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty. | 9,10 |
| 35 | | | | |
| 36 | | | | |
| 37 | | | | |
| 38 | | | | |
| 39 | | | | |
| 40 | | | | |
| 41 | | | | |
| 42 | | | | |
| 43 | Results | | | |
| 44 | Study parameters | 18 | Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended. | 10-15 |
| 45 | | | | |
| 46 | | | | |
| 47 | | | | |
| 48 | | | | |
| 49 | | | | |
| 50 | Incremental costs and | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | 10-15 |
| 51 | outcomes | | | |
| 52 | | | | |
| 53 | | | | |
| 54 | | | | |
| 55 | Characterising | 20a | <i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact | 12-14 |
| 56 | uncertainty | | | |
| 57 | | | | |
| 58 | | | | |
| 59 | | | | |
| 60 | | | | |

| | | | |
|--|-----|--|-------|
| | | of methodological assumptions (such as discount rate, study perspective). | |
| | 20b | <i>Model-based economic evaluation</i> : Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | N.A. |
| Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | N.A. |
| Discussion | | | |
| Study findings, limitations, generalisability, and current knowledge | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | 15-19 |
| Other | | | |
| Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | 19 |
| Conflicts of interest | 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations. | 19 |

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

The citation for the CHEERS Task Force Report is:
 Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. *Value Health* 2013;16:231-50.

BMJ Open

Return-to-work intervention versus usual care for sick-listed employees: health-economic investment appraisal alongside a cluster randomised trial

| | |
|---------------------------------|---|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2017-016348.R2 |
| Article Type: | Research |
| Date Submitted by the Author: | 14-Sep-2017 |
| Complete List of Authors: | Lokman, Suzanne; Trimbos-institute, Public Mental Health Volker, Danielle; Trimbos-institute Zijlstra-Vlasveld, Moniek; Trimbos-institute, Public Mental Health Brouwers, Evelien; Tilburg University Tilburg School of Social and Behavioral Sciences Boon, Brigitte; Trimbos-institute, Center of Innovation Beekman, Aartjan; EMGO Institute for Health and Care Research; VU University Medical Center Amsterdam, Department of Psychiatry Smit, Filip; Trimbos-institute, Public Mental Health; VU University Medical Centre, Department of Epidemiology and Biostatistics Van der Feltz-Cornelis, Christina; 7GGZ GGZ Breburg, TopClinical Centre for Body, Mind and Health; Tilburg University Tilburg School of Social and Behavioral Sciences, Tranzo |
| Primary Subject Heading: | Occupational and environmental medicine |
| Secondary Subject Heading: | Health economics |
| Keywords: | mental disorder, absenteeism, return to work, eHealth, cost-benefit, occupational health |
| | |

SCHOLARONE™
Manuscripts

1
2
3 1 **TITLE PAGE**4
5 2
6 3 **Return-to-work intervention versus usual care for sick-listed employees: health-**
7 4 **economic investment appraisal alongside a cluster randomised trial**8
9 5
10 6 Suzanne Lokman, Danielle Volker, Moniek C Zijlstra-Vlasveld, Evelien PM Brouwers, Brigitte
11 7 Boon, Aartjan TF Beekman, Filip Smit, Christina M van der Feltz-Cornelis12 8
13 9 Trimbos-institute, Netherlands institute of mental health and addiction, Department of Public
14 10 Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands, Maastricht University,
15 11 Department of Health Services Research, CAPHRI School of Public Health and Primary Care, PO
16 12 Box 616, 6200 MD Maastricht, The Netherlands Suzanne Lokman
17 13 economist18 14 Trimbos-institute (Netherlands institute of mental health and addiction), Department of Public
19 15 Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands, Tilburg University, School of
20 16 Social and Behavioral Sciences, Department Tranzo, PO Box 90153, 5000 LE Tilburg, The
21 17 Netherlands Daniëlle Volker
22 18 psychologist23 19 Trimbos-institute, Netherlands institute of mental health and addiction, Department of Public
24 20 Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands Moniek C Zijlstra-Vlasveld
25 21 psychologist26 22 Tilburg University, School of Social and Behavioral Sciences, Department Tranzo, PO Box
27 23 90153, 5000 LE Tilburg, The Netherlands Evelien P.M. Brouwers
28 24 psychologist29 25 Trimbos-institute, Netherlands institute of mental health and addiction, Department of Public
30 26 Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands Brigitte Boon
31 27 head of Center of Innovation32 28 Department of Psychiatry and Amsterdam Public Health research institute, VU University
33 29 Medical Center, AJ Ernststraat 1187,1081 HL Amsterdam, The Netherlands Aartjan TF
34 30 Beekman

35 31 professor of psychiatry

36 32 Trimbos-institute, Netherlands institute of mental health and addiction, Department of Public
37 33 Mental Health, PO Box 725, 3500 AS Utrecht, The Netherlands, Department of Clinical, Neuro
38 34 and Developmental Psychology, and Department of Epidemiology and Biostatistics, Amsterdam
39 35 Public Health research institute, VU University Medical Center, Van der Boechorststraat 1, 1081
40 36 BT Amsterdam, The Netherlands Filip Smit
41 37 professor of public mental health
42 38

1
2
3 1 Tilburg University, School of Social and Behavioral Sciences, Department Tranzo, PO Box
4 2 90153, 5000 LE Tilburg, The Netherlands, Clinical Centre of excellence for Body Mind and
5 3 Health, GGz Breburg, PO Box 90153, 5000 LE Tilburg, The Netherlands Christina M. van der
6 4 Feltz-Cornelis
7 5 professor of social psychiatry
8
9
10

11 6
12 7 Correspondence to: slokman@trimbos.nl, 0031-302959385 (T), 0031-302971111 (F)
13 8

14 9 Key words: mental disorders, absenteeism, return to work, eHealth, cost-benefit, occupational
15 10 health

16 11 Word count: 5268; Number of figures: 1; Number of tables: 4; Number of references: 45
17 12 Number of supplementary files for online only publication: 0
18
19
20

21 13
22 14
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 1 **Return-to-work intervention versus usual care for sick-listed employees: health-**
4 2 **economic investment appraisal alongside a cluster randomised trial**

5
6 3 **ABSTRACT**

7
8 4
9 5 **OBJECTIVE:** To evaluate the health-economic costs and benefits of a guided eHealth
10 6 intervention (ECO) encouraging sick-listed employees to a faster return to work.
11 7

12 8
13 9 **DESIGN:** A 2-armed cluster randomised trial with occupational physicians (OPs) (n=62),
14 10 clustered and randomised by region into an experimental and a control group, to conduct a
15 11 health-economic investment appraisal. Online self-reported data were collected from
16 12 employees at baseline, after 3, 6, 9 and 12 months.
17 13

18 14
19 15 **SETTINGS:** Occupational health care in the Netherlands.
20 16

21 17
22 18
23 19 **PARTICIPANTS:** Employees from small-sized and medium-sized companies (≥ 18 years),
24 20 sick-listed between 4 and 26 weeks with (symptoms of) common mental disorders visiting
25 21 their OP.
26 22

27 23
28 24 **INTERVENTIONS:** In the intervention group, employees (N=131) received an eHealth module
29 25 aimed at changing cognitions regarding return to work, while OPs were supported by a
30 26 decision aid for treatment and referral options. Employees in the control condition (N=89)
31 27 received usual sickness guidance.
32 28

33 29
34 30 **OUTCOMES MEASURES:** Net-benefits and return on investment based on absenteeism,
35 31 presenteeism, health care use, and quality adjusted life years (QALYs) gained.
36 32

37 33
38 34 **RESULTS:** From the employer's perspective, the incremental net-benefits were €3,187 per
39 35 employee over a single year, representing a return of investment of €11 per invested Euro,
40 36 with a break-even point at six months. The economic case was also favourable from the
41 37 employee's perspective, partly because of QALY health gains. The intervention was costing
42 38 €234 per employee from a health service financier's perspective. The incremental net-benefits
43 39 from a social perspective were €4,210. This amount dropped to €3,559 in the sensitivity
44 40 analysis trimming the 5% highest costs.
45 41

46 42
47 43 **CONCLUSIONS:** The data suggest that the ECO intervention offers good value for money for
48 44 virtually all stakeholders involved, because initial investments were more than recouped within
49 45 a single year. The sometimes wide 95% confidence intervals suggest that the costs and
50 46 benefits are not always very precise estimates and real benefits could vary considerably.
51 47
52 48
53 49
54 50
55 51
56 52
57 53
58 54
59 55
60 56

1
2
3 1
4 2 **TRIAL REGISTRATION:** Netherlands Trial Register NTR2108
5
6 3
7 4

8 5 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
9 6

- 10 7
- 11 • This study adds to the few available studies that present a trial-based investment
12 appraisal of the economic costs and benefits of a return to work intervention for sick-
13 listed employees
14 9
 - 15 • The trial was only powered to test a difference in sickness absence duration and not for
16 10 testing economic hypotheses.
17 11
 - 18 • The follow-up time is limited to 12 months.
19 12
- 20 13
21 14

22 15 **INTRODUCTION**
23 16

24 17 Long-term sickness absence has a significant economic impact, largely due to the substantial
25 18 productivity losses.[1, 2] Mental disorders are a leading cause of sickness absence,[3-6] which
26 19 is not without economic ramifications.[7] Common mental disorders, specifically depression
27 20 and anxiety, are the most prevalent in the workforce.[8]
28 21

29 22 For the treatment of common mental disorders a range of psychological and pharmaceutical
30 23 interventions have been shown to be effective and cost-effective.[9, 10] However,
31 24 symptomatic recovery does not automatically reduce sickness absence.[10-12] To improve
32 25 occupational outcomes it is also important to pay attention to return to work during treatment.
33 26

34 27 In the Netherlands, treatment and sickness certification are separated from each other in
35 28 social security legislation. Occupational physicians (OPs) play a central role in the sickness
36 29 guidance of workers by making a problem analysis and giving advice on a return to work plan,
37 30 whereas treatment is provided by the mental health sector. The legislation was introduced to
38 31 protect the worker's privacy and to the possibility for the worker to maintain a confidential
39 32 relationship with the curative physician.[13, 14] A guideline has been developed to suggest
40 33 directions to OPs to better assist employees with mental health problems in the return to work
41 34 process. According to this guideline, the OPs need to closely monitor both the mental health
42 35 problems and the level of functioning. When recovery is slow or hampered, they can consult or
43 36 refer to a psychiatrist, a psychologist or a social worker.[15] A study of Rebergen and
44 37 colleagues suggested that better adherence to the guideline is associated with earlier return to
45 38 work.[16] However, in practice, adherence appears to be far from optimal,[17, 18] and there
46 39 is often a lack of cooperation between the OPs and treatment providers in the mental health
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 1 sector. Several attempts have been made to bridge this gap. One study about the effect of
4 2 psychiatric consultation for OPs assisting sick-listed employees did provide results in terms of
5 3 earlier return to work.[19] However, this study was small. Another study evaluating active
6 4 treatment by an OP within a collaborative care arrangement did improve depressive
7 5 symptoms, but failed to speed up return to work.[20] It appeared that OPs need support in
8 6 helping sick-listed employees change their attitude towards resuming work and that OPs
9 7 should monitor symptom improvement and work performance in a more systematic manner.
10 8

11 9 To overcome these problems and to better manage the return to work of sick-listed employees
12 10 with (symptoms of) common mental disorders, the "E-health module embedded in
13 11 Collaborative Occupational health care" (ECO) intervention was developed. The ECO
14 12 intervention was designed to promote return to work by improving work functioning in
15 13 employees, providing a decision aid for the OP who gives guidance to the employee, and by
16 14 including the opportunity for psychiatric consultation to the OP.[21]
17 15

18 16 The results of a recent trial showed that ECO led to an earlier return to work than usual care
19 17 (mean duration of 50 days in the ECO group versus 77 days in the CAU group) and higher
20 18 remission rates of common mental disorder after 9 months in a group of sick-listed employees
21 19 with (symptoms of) mental disorders.[22]
22 20

23 21 Taking the economic perspective, we expect that the ECO intervention is cost-effective as seen
24 22 from the employer's viewpoint, because ECO is a low cost self-help intervention with a limited
25 23 amount of support from the OP and appears to be effective in reducing absenteeism. There is
26 24 less certainty how cost-effective the intervention would be as seen from the perspective of the
27 25 sick-listed employees and the health care financier (i.e. health care insurance company in the
28 26 Dutch context). Therefore, this study conducts a costs-benefit analysis of the ECO intervention
29 27 from all three stakeholders' viewpoints, and combines these in an overarching societal
30 28 perspective. These analyses are important because very few trial-based economic evaluations
31 29 have been conducted with regard to return-to-work interventions for sick-listed employees
32 30 with (symptoms of) common mental disorders.[12, 23]
33 31

34 32 **METHOD**

35 33

36 34 **Study design**

37 35 The ECO study was designed as a 2-armed cluster randomised controlled trial, with
38 36 randomisation at the level of the OP. OPs were either randomised to usual care alone or usual
39 37 care plus the ECO intervention. The Netherlands Organization for Health Research and
40 38 Development funded the study (grant number 171002403 ZonMw Doelmatigheid) together
41 39
42 40
43 41
44 42
45 43
46 44
47 45
48 46
49 47
50 48
51 49
52 50
53 51
54 52
55 53
56 54
57 55
58 56
59 57
60 58

1
2
3 1 with Achmea, a Dutch insurance company. The Medical Ethics Committee of the University
4 2 Medical Center Utrecht approved the study protocol in 2011, and the trial was registered at the
5 3 Netherlands Trial Register (NTR) under number 2108. The design of the study is described in
6 4 detail elsewhere.[21, 22] Here, we provide a brief summary of the main characteristics and
7 5 focus on the economic aspects.
8
9
10 6

7 **Randomisation**

13 8 To prevent contamination, cluster randomisation took place at the area level of the OPs
14 9 working in the same region across a total of twelve regions. An independent statistician
15 10 randomised six regions to the ECO condition and the remainder to the control condition using
16 11 computer-generated randomisation. Since the OPs had to offer the intervention, they could not
17 12 be blinded for randomisation. The researchers and participants were informed about the
18 13 allocation after the randomisation procedure.
19
20
21
22 14

23 15 **Participants**

24 16 Participants were recruited from July 2011 to January 2013 from all-cause sick-listed
25 17 employees working at small-sized and medium-sized companies in the Netherlands who visited
26 18 an OP. To be eligible for inclusion the employees had to be at least 18 years of age and on
27 19 sickness absence between 4 and 26 weeks. This time window was chosen to avoid including
28 20 employees with spontaneous recovery and to increase the probability of employees ever
29 21 returning to work.[24] In addition, the employees needed to have a score ≥ 10 on either the
30 22 depression or the somatization scale of the Patient Health Questionnaire (PHQ-9),[25, 26] or
31 23 the Generalized Anxiety Disorder questionnaire (GAD-7).[27] Exclusion criteria were (1) poor
32 24 command of the Dutch language, (2) pregnancy, (3) not having access to the Internet, (4)
33 25 being involved in a legal action against the employer.
34
35
36
37
38
39
40 26

41 27 **Procedure**

42 28 Initially an independent statistician randomised 12 regions to either CAU (6 regions with 30
43 29 OPs) or ECO (6 regions with 32 OPs) by using a computer algorithm. Within the cluster of CAU
44 30 regions 5,875 sick-listed employees were screened for eligibility resulting in 326 screen-
45 31 positives. In the cluster of ECO regions, 537 screen-positives were obtained from 8740 sick-
46 32 listed employees. Of these, 89 consenting participants received sickness guidance from OPs
47 33 who were randomised to CAU and 131 participants from OPs in the ECO cluster. The unequal
48 34 distribution of participants over the conditions was due to the cluster randomisation of the OPs.
49 35 Participants received measurements at baseline and at 3, 6, 9 and 12 months post baseline.
50 36 Dropout occurred in both conditions (see figure 1).
51
52
53
54
55
56
57
58
59
60

38 Figure 1. Flowchart of the participants

1
2
3 1
4 2 **Intervention**
5
6 3 ECO consists of 2 components: (1) the eHealth module Return@Work for the employee and (2)
7 4 an email-based decision-aid to support the OP. Return@Work is aimed at improving the self-
8 5 efficacy of employees and promoting the employee's intention to return to work. Recent
9 6 studies have shown that these factors are predictors of actual work resumption.[28-30] The
10 7 decision-aid provides the OPs with advice regarding treatment and referral options based on
11 8 the employee's outcome monitoring in Return@Work.
12 9

13
14
15
16 10 The eHealth module starts with an assessment questionnaire. Depending on the results of the
17 11 questionnaire regarding symptoms and cognitions about return to work of the individual
18 12 employee, Return@Work presented specific modules and sessions. As a consequence, the
19 13 amount of modules and sessions offered to the employees differed. In total, Return@Work
20 14 included 5 modules composed of 16 sessions, covering: 1) psycho-education, 2) cognitions
21 15 regarding return to work while having symptoms (based on principles of cognitive behavioural
22 16 therapy), 3) problem solving skills, 4) pain and fatigue management and reactivation, and 5)
23 17 relapse prevention. The employees went through the modules independently, but had the
24 18 possibility to discuss Return@Work modules and assignments with the OP. The OPs were
25 19 requested to inquire about the employee's progress in the eHealth module and to provide
26 20 support if necessary during their regular face-to-face contacts with the employee. Periodic
27 21 visits between the employee and the OP are part of the guidelines of the Dutch Board for
28 22 Occupational Medicine (NVAB),[15] to which all OPs were required to adhere.
29 23

30
31
32
33
34
35
36 24 Besides the modules, Return@Work also contained a monitor of functioning and symptoms on
37 25 a regular basis. This monitor was used for the second component of ECO, a decision aid to
38 26 support OPs in the sickness guidance of employees. Based on the outcomes of the monitor in
39 27 Return@Work the OPs received automated email messages with advice for next steps in
40 28 collaborative care. In addition, the decision aid gave OPs the option to consult a psychiatrist in
41 29 case insufficient progress was made. The OPs in the experimental condition received a 4-hour
42 30 training about ECO.
43 31

44
45
46
47
48 32 In the control condition the employees received usual sickness guidance. The guidelines of the
49 33 NVAB were used as a protocol.[15] As there is a lack of adherence to the guidelines,[17,18]
50 34 actual care was assessed with a questionnaire by all of the participating employees.
51 35

52 36 **Outcome measures**

53
54
55 37 Participants filled in the Medical Technology Assessment Cost Questionnaire for Psychiatry
56 38 (TiC-P),[31] which amongst health care use also measures absenteeism from work, which is
57
58
59
60

1 the main outcome variable of this study. The TiC-P is based on self-report and to crosscheck
2 the number of work days lost to absenteeism we compared the self-reports with administrative
3 data (see Sensitivity Analysis below). Total follow-up time was 12 months with measurements
4 at baseline and after 3, 6, 9 and 12 months. Finally, health gains in terms of quality adjusted
5 life years (QALYs) were assessed using the EuroQoL-5D-3L,[32] with the Dutch tariff.[33]

6 7 **Resource use and costing**

8 Cost data were collected using the TiC-P, including (1) direct medical costs, including the costs
9 of medication, (2) direct non-medical costs (patients' out-of-pocket costs for trips to health
10 services), (3) costs stemming from productivity losses owing to absenteeism and
11 presenteeism, and (4) costs that occurred in the domestic realm (help for housekeeping from
12 family, friends or hired people). Standard costs, expressed in euro (€), were indexed for the
13 reference year 2011 using the consumer price index from Statistics Netherlands. Costs were
14 not discounted because the follow-up period did not exceed one year.

15 16 **Computation of costs**

17 The set costs of the ECO intervention are €300 per user, which is its current (post trial) rate.
18 Direct medical costs are limited to mental health service use. The medical costs were
19 computed by multiplying the number of health service units (sessions, visits, hospital days)
20 with their standard full economic cost price.[34] Only medication costs for mental problems
21 were included in the economic analysis. For every type of drug (e.g. antidepressants,
22 benzodiazepines, antipsychotics, hypnotics) an average cost price was calculated based on the
23 cost prices per standard daily dose of three drugs most often prescribed to the participants as
24 reported in the Pharmaceutical Compass,[35] while taking into account the GP's prescription
25 costs, the pharmacist's dispensing costs and the pharmacist's claw back as per the guideline
26 for cost computations in health care.[34]

27
28 The direct non-medical costs consisted of the travel costs that participants had to make to visit
29 OPs and health services. These costs were calculated as the average distance to the specific
30 health service provider multiplied by the costs per km (€0.21) plus parking costs (€3.11) per
31 hour. To the direct non-medical costs we added the costs of (informal) caregivers (e.g. family
32 and friends) due to the employee's reduced functionality at home, computed by multiplying the
33 number of hours by €12.96.

34
35 In the Netherlands QALY health gains are valued at €50,000 per QALY with a range between
36 €20,000 and €80,000.[36] We used the lower bound of €20,000 to conduct our analysis under
37 conservative assumptions.

1
2
3 1 Productivity losses comprised the costs of lost workdays due to absenteeism and the costs of
4 2 inefficiency while at work (presenteeism). We used the human capital method to value the
5 3 productivity costs.[37] In the case of absenteeism, this method multiplies the number of days
6 4 absent by the gender and age-specific average gross wages per employee, as per the Dutch
7 5 guideline for health economic evaluation.[34] To assess the costs of presenteeism we used the
8 6 number of days actually worked when ill multiplied by a self-reported inefficiency score. This
9 7 score ranged from 0 (as effective as in good health) to 1 (totally ineffective). Again, the
10 8 gender and age-specific average gross wages were used to compute the costs of presenteeism.
11 9 To illustrate, if an employee reported an inefficiency score of 0.50 for 7 working days then we
12 10 assumed that 3.5 working days have been lost due to presenteeism.
13
14
15
16
17
18
19

20 12 **Analyses**

21 13 Following recommendations from the CONSORT and CHEERS statements,[38-40] analyses
22 14 were conducted in agreement with the intention to treat principle. Therefore all participants as
23 15 randomised were retained in the analysis and missing observations due to dropout were
24 16 imputed. For imputation we used both the estimation-maximisation (EM) algorithm as
25 17 implemented in SPSS for the main analysis, and regression imputation (RI) as implemented in
26 18 Stata for the sensitivity analysis (see below). In both imputation strategies we used predictors
27 19 of outcomes (costs and QALYs) and predictors of dropout (age, gender, partner status, country
28 20 of birth, number of work loss days). Predictors of the outcomes were included to increase
29 21 precision in the imputed values, predictors of dropout were incorporated to tackle selection-
30 22 bias, if any, and to meet the missing at random (MAR) assumption underlying most imputation
31 23 techniques.
32
33
34
35
36
37

38 25 The economic evaluation was conducted as an incremental cost-benefit analysis, because the
39 26 primary outcome (duration of sick leave) could directly be expressed in terms of monetary
40 27 benefits. The costs and benefits were calculated at baseline, 3, 6, 9 and 12 months in the ECO
41 28 and CAU conditions. The costs in the intermediate months were linearly interpolated. This
42 29 allowed mapping the monthly cash flows of costs and benefits over the full 12-month period.
43 30 The cash flows were computed from four perspectives: (1) the employer's perspective
44 31 focussing on the net-benefits from greater productivity via lesser absenteeism and lesser
45 32 presenteeism; (2) the health care payer's perspective (in the Netherlands: health care
46 33 insurers) focussing on the direct medical costs due to health service use, including the costs of
47 34 medication, (3) the employee's perspective focussing on QALY health gains, fewer out-of-
48 35 pockets costs and less informal care from family members or friends. Finally, we included the
49 36 societal perspective (4), including all costs and benefits, regardless of who incurs costs or
50 37 receives benefits.
51
52
53
54
55
56
57
58
59
60

1
2
3 1 The monthly cash flows were used to compute the cumulative costs and cumulative monetary
4 2 benefits over the full twelve months. Incremental costs, incremental benefits and incremental
5 3 net-benefits were obtained by comparing ECO intervention with CAU. These are the main
6 4 outcomes of the economic analysis alongside metrics such as the break-even point and the
7 5 return on investment (ROI).
8
9

10 6
11 7 For assessing the incremental net-benefits we relied on non-parametric bootstrapping (2,500
12 8 replications) since costs are non-normally distributed. Statistics such as mean costs, 95%
13 9 confidence intervals, standard errors and p-values are all based on non-parametric
14 10 bootstrapping to increase the robustness of our findings. The data were analysed in SPSS
15 11 (version 22) and Stata (version 13.1).
16
17
18
19
20

21 **Sensitivity analysis**

22 14 The main analysis (using the overarching societal perspective and based on EM imputation)
23 15 was repeated three times in a series of sensitivity analyses. Firstly, the analysis was conducted
24 16 again, but now based on regression imputation (RI) to assess the robustness of the findings
25 17 under a different imputation technique. Secondly, we crosschecked the self-reported
26 18 absenteeism against administrative data derived from the registers of the occupational health
27 19 service or the employer, because the main analysis was based on self-reports and some recall
28 20 bias (underreporting) could have occurred. Finally, we recalculated the incremental net-
29 21 benefits after trimming the highest 5% of total cumulative costs per employee, because the
30 22 participants with the extremely high costs were only a small minority but may have exercised
31 23 a disproportional influence on the cost estimates and pushed outcomes to a more favourable
32 24 outcomes for the ECO intervention. By excluding these participants, primarily from the CAU
33 25 condition, the net-benefits were re-estimated but now under conservative assumptions.
34
35
36
37
38
39
40

41 **RESULTS**

42 43 44 29 **Sample characteristics and baseline costs**

45 30 Baseline characteristics of the sample (including baseline costs) are presented in table 1. The
46 31 mean age of the 220 participants was 44 years and 59% was women. No important differences
47 32 were observed at baseline in demographic characteristics and quality of life, but baseline costs
48 33 were somewhat higher in the ECO condition, suggesting that the ECO group had a slightly
49 34 disadvantageous start. We will return to this issue in the Discussion. As described by Volker
50 35 and colleagues,[22] job characteristics and sickness absence duration at baseline were also
51 36 comparable between the intervention condition and control condition, indicating that the
52 37 randomisation was generally well balanced.
53
54
55
56
57
58
59
60

1
2
3 1 Table 1. Baseline characteristics in the care as usual (CAU) and the ECO intervention group

| | CAU (n=89) | ECO (n=131) |
|--|--------------|--------------|
| Age, mean (SD) | 45.5 (10.7) | 43.3 (9.5) |
| Female, N (%) | 53 (59.6) | 77 (58.8) |
| Married/living together, N (%) | 62 (69.7) | 91 (69.5) |
| Educational level, N (%) | | |
| Low | 32 (36.0) | 48 (36.6) |
| Average | 31 (34.8) | 47 (35.9) |
| High | 26 (29.2) | 36 (27.5) |
| Country of birth: The Netherlands, N (%) | 83 (93.3) | 123 (93.9) |
| Direct medical costs, mean (SD) | 645 (58) | 602 (49) |
| Direct non-medical costs, mean (SD) | 35 (2) | 33 (2) |
| Absenteeism, mean (SD) | 2850 (146) | 3078 (125) |
| Presenteeism, mean (SD) | 34 (16) | 20 (14) |
| Costs in the domestic realm, mean (SD) | 143 (26) | 133 (20) |
| Medication, mean (SD) | 8 (2) | 12 (3) |
| Total costs, mean (SD) | 3716 (154) | 3879 (141) |
| Quality of life, mean (SD) | 0.57 (0.027) | 0.54 (0.024) |

29
30 2
31 3 **Loss to follow-up**

32 4 The measurements at 3, 6, 9 and 12 months were completed by 155 (70.5%), 157 (71.4%),
33 5 134 (60.9%) and 128 (58.2%) of the participants. The dropout rate over the 12-month trial
34 6 period was higher in the ECO condition (45.0%) than the control condition (37.1%), but this
35 7 difference was not statistically significant ($\chi^2=1.38$; $df=1$; $p=0.240$). As indicated, we looked
36 8 for variables that predict dropout and included these as predictors in the EM and IR
37 9 imputations. This was done to counter selection-bias (if any) and to better meet the MAR
38 10 assumption underpinning the imputation strategies.

39 11
40 12 On the topic of treatment adherence, 90 of the 131 participants in the ECO condition (69%)
41 13 finished the introduction and started with the intervention. These participants had a mean-
42 14 number of total log-ins of 7.8. Forty percent (36/90) completed at least half of the modules
43 15 and 23% (21/90) finished at least 70% of the prescribed number of sessions.[22]

44 16
45 17 **Costs and QALYs at 3, 6, 9 and 12 months**

46 18 The next step of the cost benefit analyses was to ascertain costs and quality of life at the
47 19 follow-up measurements (Table 2). Cost differences were highest for absenteeism. At 12
48 20 months all the cost differences were statistically significant and in favour of the ECO condition.

1 The total costs difference at the 12 month follow-up amounted to €919 (SE=205; z=4.48;
2 p<0.001), mainly due to reduced absenteeism.

3
4 Table 2. Average monthly costs in the care as usual (CAU) and the ECO intervention group at
5 3, 6, 9 and months (in 2011 Euro)^{1, 2}

| | 3 months | 6 months | 9 months | 12 months |
|----------------------------------|----------|----------|----------|-----------|
| Direct medical costs | | | | |
| CAU | 474 | 321 | 383 | 296 |
| ECO | 463 | 476 | 333 | 148 |
| Cost difference | 11 | -155 | 50 | 148 |
| Direct non-medical costs | | | | |
| CAU | 135 | 74 | 102 | 98 |
| ECO | 104 | 89 | 67 | 45 |
| Cost difference | 31 | -15 | 35 | 53 |
| Productivity losses | | | | |
| Absenteeism | | | | |
| CAU | 2120 | 1699 | 1276 | 1118 |
| ECO | 1887 | 1264 | 725 | 572 |
| Cost difference | 233 | 435 | 551 | 546 |
| Presenteeism | | | | |
| CAU | 166 | 233 | 269 | 493 |
| ECO | 357 | 408 | 322 | 325 |
| Cost difference | -191 | -175 | -53 | 168 |
| Total costs | | | | |
| CAU | 2895 | 2328 | 2029 | 2005 |
| ECO | 2811 | 2238 | 1446 | 1090 |
| Cost difference | 84 | 90 | 583 | 915 |
| Quality of life (utility) | | | | |
| CAU | 0.65 | 0.68 | 0.68 | 0.73 |
| ECO | 0.65 | 0.72 | 0.76 | 0.77 |
| Difference in utilities | 0 | 0.04 | 0.08 | 0.04 |

6
7 1 Between-group differences in italics are statistically significant at p<0.05.

8 2 Numbers may not add due to rounding

1 **Cost-benefit analysis: employer's perspective**

2 For the employer's perspective only the intervention costs and costs stemming from
 3 absenteeism and presenteeism were included, thus assuming that the employer would be
 4 interested to know the pay out of this investment when paying for the intervention. Cumulated
 5 over the 12-months period the incremental benefits were €3,487 in favour of the ECO
 6 condition (Bootstrapped 95% CI= -418~7,390; SE=1,992; z=1.75; p=0.080), which was
 7 mainly due to a larger reduction in absenteeism over 12 months compared to care as usual
 8 (bootstrapped M=4,291; 95% CI= 290~8,292; SE=2,041; z=2.10; p=0.036). Next, we
 9 calculated incremental net-benefits, by subtracting the intervention costs (€300) from the
 10 incremental benefits. As shown in table 3 the incremental net-benefits over twelve months
 11 were €3,187 per employee in favour of the ECO condition, but there is significant uncertainty
 12 in the estimate (Bootstrapped 95% CI=-656~7,029; SE=1,961; z=1.63; p=0.104). We return
 13 to this issue in the Discussion. The break-even point for the employer, the moment in time
 14 where the investment of €300 is recouped, is around six months. The return of investment
 15 (ROI) is $3,187/300=10.62$, indicating that for every euro invested the pay-out is €10.6.

16
 17 Table 3. Monthly per patient costs in the care as usual (CAU) and the ECO intervention group
 18 from an employer's perspective (in 2011 Euro)

| Month | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | Cumulative |
|--------------------------|------|------|------|------|------|------|------|------|------|------|------|------|------------|
| CAU | | | | | | | | | | | | | |
| Absenteeism | 2850 | 2485 | 2120 | 1910 | 1910 | 1699 | 1487 | 1487 | 1276 | 1197 | 1197 | 1118 | 20736 |
| Presenteeism | 34 | 100 | 166 | 199 | 199 | 233 | 251 | 251 | 269 | 380 | 380 | 493 | 2955 |
| Total costs | 2884 | 2585 | 2286 | 2109 | 2109 | 1932 | 1738 | 1738 | 1545 | 1577 | 1577 | 1611 | 23691 |
| ECO | | | | | | | | | | | | | |
| Absenteeism | 3078 | 2483 | 1887 | 1576 | 1576 | 1264 | 994 | 994 | 725 | 648 | 648 | 572 | 16445 |
| Presenteeism | 20 | 188 | 357 | 382 | 382 | 408 | 365 | 365 | 322 | 323 | 323 | 325 | 3760 |
| Total costs | 3098 | 2671 | 2244 | 1958 | 1958 | 1672 | 1359 | 1359 | 1047 | 971 | 971 | 897 | 20205 |
| Incremental benefits | -214 | -86 | 42 | 151 | 151 | 260 | 379 | 379 | 498 | 606 | 606 | 714 | 3486 |
| Intervention costs | -300 | | | | | | | | | | | | |
| Incremental net-benefits | -514 | -600 | -558 | -407 | -256 | 4 | 383 | 762 | 1260 | 1866 | 2472 | 3186 | |
| Return on investment | 10.6 | | | | | | | | | | | | |

19
 20 **Cost-benefit analysis: health care payer's perspective**
 21 For the perspective of the health care financier we looked at the direct medical costs including
 22 the costs for medication. We computed the monthly cash flows and compared these between
 23 the ECO and CAU conditions as before. The cumulative costs over twelve months were more or
 24 less the same for each condition with a small difference of €66 in favour of the ECO condition.
 25 Assuming that the health insurer would pay for the intervention, the intervention costs of €300

1
2
3 1 have to be subtracted from these benefits in order to obtain the net-benefits. This generated a
4 2 negative value of €234, implying that the ECO intervention is not cost saving from a health
5 3 care insurer's perspective (bootstrapped 95% CI=-1,379~911; SE=584; z=-0.40; p=0.689).

5 **Cost-benefit analysis: employee's perspective**

6 Employee's costs and benefits included direct non-medical costs (i.e. the patient's out-of-
7 pocket costs and costs in the domestic realm) and QALY health gains. Cumulated over twelve
8 months the incremental benefits for the ECO group were €262 regarding non-medical costs
9 and €696 due to QALY gains (0.035*€20,000). The incremental net-benefits were €958-€300=
10 658 (bootstrapped 95% CI=290~1,025; SE=187; z=3.51; p=0.000). The break-even point
11 occurred at eight months and the return on investment was 658/300=2.2.

13 **Cost-benefit analysis: societal perspective**

14 For the societal perspective we included the costs and benefits of all stakeholders. The
15 difference between conditions of the cumulative benefits was €29,893-€25,383=€4,510 in
16 favour of the intervention condition (bootstrapped 95% CI= 103~8,918; SE=2,249; z=2.01
17 p=0.045). Subtraction of the intervention costs of €300 yielded incremental net-benefits from
18 a social perspective of €4,210 (bootstrapped 95% CI= -259~8,674; SE=2,2277; z=1.85;
19 p=0.064). Break-even was achieved at seven months and the return on investment was
20 4,233/300= 14.0.

22 **Sensitivity analyses**

23 For the main analysis we used EM imputation; now we recomputed the estimates under
24 regression imputation (RI). Taking the societal perspective, the incremental net-benefits
25 became €4,093 (Bootstrapped 95% CI= -279~8,465; SE=2,231; z=1.83; p=0.067) and the
26 return on investment 4,093/300=13.6, which is close to the EM-based analysis (see table 4).

27
28 The incremental net-benefits in the main analyses were dominated by the costs offsets due to
29 reduced absenteeism, but these were based on self-reported data. Crosschecking the self-
30 reported data against administrative data derived from the registers of the occupational health
31 service or employer showed that the estimates for days absent were lower in the analysis
32 based on self-report data than on administrative data (72 work days absent based on self-
33 reported data versus an average of 102 work days absent based on administrative data).
34 When basing the analysis on administrative data, the total cumulative incremental net-benefits
35 became €5,316 (Bootstrapped 95% CI=-2,590~13,222; SE=4,034; z=1.32; p=0.188), which
36 is higher by a factor 1.3 than the corresponding estimate presented in the main analysis. The
37 main analysis thus represents a safer (lower) estimate.

1
2
3 1 Finally, we repeated the main analysis by replacing the total costs of the respondents with the
4 2 top 5% highest total costs due to absenteeism by the highest amount witnessed in the other
5 3 95% respondents. The top 5% outliers were mainly situated in the CAU condition, raising the
6 4 average costs for this group. The incremental net-benefits based on the trimmed costs
7 5 dropped from €4,210 to €3,559 (SE 95% CI= -611~7,729; SE=2,128; z=1.67; p=0.094),
8 6 which can be regarded as a more conservative lower bound.
9 7

8 Table 4. Incremental net-benefit and return on investment from societal perspective for base
9 case and sensitivity analyses (in 2011 Euro)

| | Incremental net-benefit | Return on investment |
|---|-----------------------------|----------------------|
| Base case analysis | 4,210 (-259 to 8,674) | 14.0 |
| sensitivity analysis regression imputation | 4,093 (-279 to 8,465) | 13.6 |
| sensitivity analysis administrative data | 5,316 (-2,590 to 13,222) | 17.7 |
| sensitivity analysis trimming highest 5% | 3,559 (-611 to 7,729) | 11.9 |

11 DISCUSSION

13 Principal findings

14 This study was set out to evaluate the cost-effectiveness of an intervention that encourages
15 sick-listed employees with (symptoms of) common mental disorders to make an early return to
16 their work. The economic evaluation was conducted as an incremental cost-benefit analysis
17 and reports on the incremental cost to benefit ratio, the return on investment, the break-even
18 point, and the incremental monetary net-benefits, as customary seen in business cases and
19 investment appraisals. These metrics were computed from various perspectives: the
20 perspective of the employer, the employee, the health care financier and society. The main
21 findings can now be summarised as follows:

- 22 • Taking the employer's perspective, the focus of the economic evaluation was placed on the
23 intervention costs and changes in productivity owing to changes in absenteeism and
24 presenteeism. Assuming that the employer would make the investment in the ECO
25 intervention of €300 per employee, the incremental net-benefits were €3,187 per employee
26 over a year. This was equivalent to a return on investment of €11 per invested Euro.
27 Benefits largely stemmed from reduced absenteeism and exceeded the investment costs
28 after six months.
- 29 • From the perspective of the health care payer the incremental net-benefits were negative,
30 amounting to additional costs of €234 per employee on average.

- 1 • As seen from the employee the net-benefits, including the value of the employee's QALY
2 health gains, exceeded the costs by €658.
- 3 • From the societal perspective, the initial investment was also more than recouped.
4 Considering all costs and benefits, but ignoring the value of QALY gains, the incremental
5 net-benefits were €4,210, with a break-even point at 7 months. Every euro invested
6 yielded €14. Trimming the 5% highest costs, mostly from the care as usual condition,
7 reduced the incremental net-benefits to €3,559.

8 9 **Limitations**

10 This study has several limitations, which are reported and discussed here.

- 11 • First, cost data are often non-normally distributed with a some people generating very high
12 costs. This results in large standard deviations in the costs estimates and less precise
13 estimates of average costs. In such a context it would require a very large sample size to
14 power the trial for testing economic hypotheses. However, our study was only powered to
15 test a difference in sickness absence duration. As a consequence, the wide 95% confidence
16 intervals indicate that the cost estimates are subject to much uncertainty. More specifically,
17 when trimming the highest 5% of the costs in one of our sensitivity analysis showed that
18 the incremental net-benefits became €3,559, which is 85% of the original estimate of
19 €4,210. This suggests that our study needs replication, preferably in a larger study.
- 20 • Second, loss-to follow up was substantial. To handle dropout, missing data were imputed
21 using estimation maximization (EM). To ascertain the robustness of our findings we also
22 used regression imputation (RI). With RI we arrived at similar conclusions: €4,093 (versus
23 €4,210 under EM), attesting to the robustness in our findings. Nonetheless, selection bias
24 introduced by (selective) dropout cannot be ruled out completely and could have influenced
25 the outcomes that we obtained.
- 26 • Third, costs at baseline were higher in the ECO condition. We could have adjusted for the
27 baseline differences, but this would most likely have led to even better outcomes in favour
28 of the ECO condition. Ignoring the baseline differences has therefore put our main analyses
29 on a more conservative footing.
- 30 • Fourth, the main driver of costs and benefits was absenteeism and in the main analysis
31 these were based on self-report. This may have introduced some recall bias, but self-
32 reports of absenteeism usually involve underreporting thus leading to conservative
33 outcomes. Still, we crosschecked the self-reports against administrative data from the
34 registers of the occupational health service and the employer. As expected, the benefits
35 were lower when based on self-reports than on administrative data.
- 36 • Fifth, it should be noted that the cost-benefit analysis did not include the future costs of
37 implementing the ECO intervention on a wider scale. As the main component is a low cost
38 self-help intervention (Return@Work) and the training of OPs only lasts a few hours, the

- 1
2
3 1 implementation costs are expected to be low, but should be considered when the
4 2 intervention is disseminated on a wider scale.
5
6 3 • Finally, the follow-up time is limited to 12 months. We do not know what the net-benefits
7 4 would be over a longer time span. However, costs differences were highest in the last
8 5 months. This may imply that a longer follow-up period would have seen more profitable
9 6 outcomes.
10 7

13 8 **Results in context**

14 9 Reviews about the effectiveness of psychological return to work interventions for employees
15 10 with mental health problems show mixed outcomes in reducing sickness absence and
16 11 promoting an earlier return to work.[12, 23] Moreover, only a few of the reviewed studies that
17 12 appeared to be effective report a full economic evaluation. Of these, none evaluated a guided
18 13 eHealth intervention for return to work. One study that is somewhat comparable with our
19 14 study is from Schene and colleagues. Schene et al describe the economic evaluation of an
20 15 intervention for employees with major depression, who were sick-listed between 10 weeks and
21 16 2 years.[41] The experimental condition received occupational therapy in addition to usual
22 17 outpatient treatment for depression. Their intervention increased the number of hours worked
23 18 accumulating in a median economic gain of US\$4000–5000 per patient per year, which is in
24 19 line with our findings regarding the reduction in absenteeism. The study of Schene et al was
25 20 smaller (n=62), was directed at a more severely depressed population, and the intervention
26 21 was not delivered online but as an intensive face-to-face therapy consisting of 24 group
27 22 sessions and 15 individual sessions.
28 23

29 24 Lerner and colleagues evaluated a brief telephonic program to improve work functioning for
30 25 employees with major depressive disorder or dysthymia with an at-work productivity loss of at
31 26 least 5% in the past two weeks.[42] Compared to usual care, annualised cost savings
32 27 averaged at \$6042 per participant but these savings were extrapolated from a shorter (4
33 28 months) follow-up. These cost savings are higher than the cost-savings observed in our study.
34 29 Nonetheless, Lerner's et al. extrapolation from 4 to 12 months might have overstated the
35 30 savings if the treatment effect was not sustained.
36 31

37 32 Arends and colleagues evaluated the costs and benefits of a problem-solving intervention
38 33 provided by OPs to prevent recurrent sickness absence in workers with common mental
39 34 disorders.[43] Compared to care as usual the intervention was more effective but also more
40 35 expensive. From an employer's perspective the intervention showed no economic benefits,
41 36 which is in contrast to our study.
42 37

1
2
3 1 Noben and colleagues conducted a cost-benefit analysis from the employer's perspective of a
4 2 preventive intervention in the work setting among nurses with an elevated-risk of mental
5 3 complaints.[44] The authors concluded that the intervention was a good investment as the
6 4 net-benefits (stemming from reduced absenteeism and presenteeism) were positive (€651)
7 5 and the return on investment was €11 per Euro spent. This return on investment is
8 6 comparable with ours.
9 7

10 8 In contrast to Noben and colleagues and several other studies [45] we found negative results
11 9 for presenteeism in the short run (first nine months), but these were alleviated in the longer
12 10 run (at the end of the year). An explanation for the initially negative results on presenteeism
13 11 might be that employees who returned to work early were not completely fit and as productive
14 12 as normally. In other words there was an initial trade-off between reduced absenteeism and
15 13 increased presenteeism. However, after the first nine months the additional costs caused by
16 14 presenteeism ceased to exist and were reversed into benefits. This change is possibly driven
17 15 by an improvement in quality of life when people work.
18 16

19 17 The literature suggests that in terms of economic costs presenteeism often is a larger problem
20 18 than absenteeism. Our results are not in line with these findings. This could be due to the
21 19 Dutch system in which employees receive a substantial percentage of their wage during the
22 20 first two years of their illness. In many other countries the fall in income is more acute when
23 21 employees stay absent from their work, increasing the incentive to keep on working – even
24 22 when work is then associated with greater levels of presenteeism.
25 23

26 24 The results of our study can only be generalised to employees who have been sick-listed for 4-
27 25 26 weeks, working in small- to medium-sized companies.
28 26

27 **Conclusions and implications**

28 28 In the Netherlands, employers have an incentive to invest in sickness management as they
29 29 have the responsibility to pay 70-100% of the salary of sick-listed employees for up to two
30 30 years. Employees who are on sickness absence have to visit an occupational physician, paid by
31 31 the employer within the first six weeks. Both the employee and employer have to agree on an
32 32 action plan. In this plan the responsibilities of both parties are defined to ensure a quick return
33 33 to work of the employee. In this context the ECO intervention can be seen as an effective
34 34 intervention that, in addition, has a high probability of offering good value for money because
35 35 the initial investment (of €300) is more than recouped within a single year as seen from the
36 36 employer's perspective, while the employee derives benefits in the form of increased quality of
37 37 life when returning to work sooner rather than later. As noted, some 95% confidence intervals
38 38 of our estimates are wide. By implication, one should not rely too much on the point estimates
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 1 of net-benefits, return on investment ratios, break-even points, because they lack precision. In
4 2 other words, our estimates have some degree of uncertainty, but suggest that the ECO
5 3 intervention has a high likelihood to be an appealing business case as seen from most
6 4 stakeholder perspectives.
7
8
9 5

10 6 **Acknowledgements**

11 7 We acknowledge with many thanks Prof.dr. H Anema (VU University) for advice on the design
12 8 of the study, Dr. G. van Lomwel (ACHMEA/UWV) for advice on design of the study and
13 9 providing access to data, and Dr. M. Blankers for help with statistical analyses.
14
15
16 10

17 11 **Contributors**

18 12 CFC initiated the collaborative clinical trial project. MZV, AB and CFC contributed to the design
19 13 of the study and obtained the funding. DV, MZV and CFC were responsible for the acquisition
20 14 of the data. SL and FS conducted the statistical analysis and drafted the first manuscript. DV,
21 15 MZV, EB, BB, AB and CFC critically revised the manuscript. All authors read and approved the
22 16 final manuscript. SL, FS and CFC are guarantors.
23
24
25
26 17

27 18 **Funding**

28 19 This study was financially supported by The Netherlands Organization for Health Research and
29 20 Development (ZonMw) (grant number 171002403) and Achmea, a Dutch health insurance
30 21 company. The funding sources had no role in the data analysis and interpretation and in the
31 22 writing of this paper.
32
33
34 23

35 24 **Competing interests**

36 25 All authors have completed the ICMJE uniform disclosure form at
37 26 www.icmje.org/coi_disclosure.pdf and declare: financial support for the submitted work from
38 27 The Netherlands Organisation for Health Research and Development (ZonMw) and from
39 28 Achmea SZ; SL, DV, MZV, BB, FS report personal fees from employment at the Trimbos
40 29 institute, the Netherlands institute of mental health and addiction, a not-for-profit
41 30 organisation, CFC has received research grants from Eli Lilly outside the submitted work.
42
43
44
45
46
47 31

48 32 **Ethical approval**

49 33 The study protocol was approved by the Medical Ethics Committee of the University Medical
50 34 Center Utrecht, The Netherlands, in February 2011. All participants provided written informed
51 35 consent before taking part.
52
53
54 36

55 37 **Transparency**

1
2
3 1 The lead author affirms that the manuscript is an honest, accurate and transparent account of
4 2 the study being reported; that no important aspects of the study have been omitted; and that
5 3 and discrepancies from the study as planned (and if relevant, registered) have been explained.
6 4

7
8
9 5 Data sharing: No additional data
10 6

11 7 **Copyright**

12 8 The Corresponding Author has the right to grant on behalf of all authors and does grant on
13 9 behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all
14 10 forms, formats and media (whether known now or created in the future), to i) publish,
15 11 reproduce, distribute, display and store the Contribution, ii) translate the Contribution into
16 12 other languages, create adaptations, reprints, include within collections and create summaries,
17 13 extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on
18 14 the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of
19 15 electronic links from the Contribution to third party material where-ever it may be located;
20 16 and, vi) licence any third party to do any or all of the above.
21 17

22 18 **Legends of figures**

23 19 Figure 1. Flowchart of the clusters and participants
24 20

25 21 **References**

- 26 22 1. Lerner D, Amick BC, Lee JC, et al. Relationship of employee-reported work limitations to
27 23 work productivity. *Med Care* 2003;41(5):649–59. doi:10.1097/01.MLR.0000062551.76504.A9.
28 24
29 25 2. Adler DA, McLaughlin TJ, Rogers WH, et al. Job performance deficits due to depression. *Am*
30 26 *J Psychiatry* 2006 Sep;163(9):1569–76. doi:10.1176/ajp.2006.163.9.1569.
31 27
32 28 3. Moncrieff J, Pomerleau J. Trends in sickness benefits in Great Britain and the contribution of
33 29 mental disorders. *J Public Health Med* 2000;22(1):59-67. doi:10.1093/pubmed/22.1.59.
34 30
35 31 4. Shiels C, Gabbay MB, Ford FM. Patient factors associated with duration of certified sickness
36 32 absence and transition to long-term incapacity. *Br J Gen Pract* 2004;54(499):86-91.
37 33
38 34 5. Cattrell A, Harris EC, Palmer KT, et al. Regional trends in awards of incapacity benefit by
39 35 cause. *Occup Med (Lond)* 2011;61(3): 148-151. doi:10.1093/occmed/kqr008 [published
40 36 Online First: 11 April 2011].
41 37
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 6. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases
4 2 and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease
5 3 Study 2010. *Lancet* 2012;380:2197-2223. doi:10.1016/S0140-6736(12)61689-4 [published
6 4 Online First: 22 February 2013].
7
8 5
9
10 6 7. de Graaf R, Tuithof M, van Dorsselaer S, et al. Sick leave due to psychological and physical
11 7 illnesses among employees: results of the 'Netherlands Mental Health Survey and Incidence
12 8 Study-2' (NEMESIS-2) [in Dutch: Verzuim door psychische en somatisch aandoeningen bij
13 9 werkenden: resultaten van de 'Netherlands Mental Health Survey and Incidence Study-2'
14 10 (NEMESIS-2)]. Utrecht: Trimbos-instituut 2011.
15 11
16 12 8. Lelliott P, Tulloch S, Boardman J, et al. Mental Health and Work. London: Cross Government
17 13 Health Work and Well-being Programme 2008.
18 14
19 15 9. Chisholm D, Sanderson K, Ayuso-Mateos JL, et al. Reducing the global burden of
20 16 depression. *Br J Psychiatry* 2004;184:393-403. doi:10.1192/bjp.184.5.393.
21 17
22 18 10. Harvey SB, Joyce S, Modini M, et al. Work and depression/anxiety disorders: a systematic
23 19 review of reviews. Melbourne, Australia: Beyondblue 2013.
24 20
25 21 11. Ejeby K, Savitskij R, Ost LG, et al. Symptom reduction due to psychosocial interventions is
26 22 not accompanied by a reduction in sick leave: results from a randomized controlled trial in
27 23 primary care. *Scand J Prim Health Care* 2014;32(2):67-72.
28 24 doi:10.3109/02813432.2014.909163 [published Online First: 17 April 2014].
29 25
30 26 12. Nieuwenhuijsen K, Faber B, Verbeek JH, et al. Interventions to improve return to work in
31 27 depressed people. *Cochrane Database Syst Rev* 2014;12:CD006237.
32 28 doi:10.1002/14651858.CD006237 [published Online First: 3 December 2014].
33 29
34 30 13. OECD (2014). Mental Health and Work: Netherlands, Mental Health and Work. Paris: OECD
35 31 Publishing. doi:10.1787/9789264223301-en.
36 32
37 33 14. Willems JHBM, Doppegieter RMS. De scheiding van 'behandeling en controle': aan
38 34 actualisering toe? *Tijdschrift voor Bedrijfs- en Verzekeringsgeneeskunde* 2007;15(4):164-
39 35 167. doi:10.1007/BF03074555.
40 36
41 37
42 38
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 15. van der Klink JJL. Richtlijn: Handelen van de bedrijfsarts bij werkenden met psychische
4 2 problemen. [Guideline: The management of mental health problems of workers by
5 3 occupational physicians] Eindhoven: NVAB [Netherlands Society of Occupational Medicine]
6 4 2000.
7
8
9
10 6 16. Rebergen DS, Bruinvels DJ, Bos CM, et al. Return to work and occupational physicians'
11 7 management of common mental health problems – process evaluation of a randomized
12 8 controlled trial. *Scand J Work Environ Health* 2010;36(6):488-498. doi:10.5271/sjweh.3084.
13
14
15
16 10 17. Rebergen D, Hoenen J, Heinemans A, et al. Adherence to mental health guidelines by
17 11 Dutch occupational physicians. *Occup Med (Lond)* 2006;56(7):461-468.
18 12 doi:10.1093/occmed/kql042 [published Online First: 16 June 2006].
19
20
21
22 14 18. Rebergen DS, Bruinvels DJ, Bezemer PD, et al. Guideline-based care of common mental
23 15 disorders by occupational physicians (CO-OP study): a randomized controlled trial. *J Occup
24 16 Environ Med* 2009;51(3):305-312. doi:10.1097/JOM.0b013e3181990d32.
25
26
27
28 18 19. Van der Feltz CM, Hoedeman R, de Jong FJ, et al. Faster return to work after psychiatric
29 19 consultation for sicklisted employees with common mental disorders compared to care as
30 20 usual. A randomized clinical trial. *Neuropsychiatr Dis Treat*. 2010;6:375–385. [published
31 21 Online First: 2 July 2010].
32
33
34
35 23 20. Vlasveld MC, van der Feltz-Cornelis CM, Adèr HJ, et al. Collaborative care for sick-listed
36 24 workers with major depressive disorder: a randomised controlled trial from the Netherlands
37 25 Depression Initiative aimed at return to work and depressive symptoms. *Occup Environ Med*
38 26 2013;70(4):223-230. doi:10.1136/oemed-2012-100793 [published Online First: 29 October
39 27 2012].
40
41
42
43
44 29 21. Volker D, Vlasveld MC, Anema JR, et al. Blended E-health module on return to work
45 30 embedded in collaborative occupational health care for common mental disorders: design of a
46 31 cluster randomized controlled trial. *Neuropsychiatr Dis Treat* 2013;9:529-537.
47 32 doi:10.2147/NDT.S43969 [published Online First: 19 April 2013].
48
49
50
51 34 22. Volker D, Zijlstra-Vlasveld MC, Anema JR, et al. Effectiveness of a Blended Web-Based
52 35 Intervention on Return to work for Sick-Listed Employees With Common Mental Disorders:
53 36 Results of a Cluster Randomized Controlled Trial. *J Med Internet Res* 2015;17(5):e116.
54 37 doi:10.2196/jmir.4097 [published Online First: 13 May 2015].
55
56
57
58
59
60

- 1
2
3 1 23. Arends I, Bruinvels DJ, Rebergen DS, et al. Interventions to facilitate return to work in
4 2 adults with adjustment disorders. *Cochrane database Syst Rev*. 2012;12:CD006389.
5 3 doi:10.1002/14651858.CD006389.pub2 [published Online First: 12 December 2012].
6 4
7 4
8 5 24. Henderson M, Glozier N, Holland EK. Long term sickness absence. *BMJ*. 2005;330:802–
9 6 803. doi: <https://doi.org/10.1136/bmj.330.7495.802> [published Online First: 07 April 2005].
10 7
11 7
12 8 25. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity
13 9 measure. *J Gen Intern Med* 2001;16(9):606-613.
14 10 doi:10.1046/j.1525-1497.2001.016009606.x [published Online First: 20 December 2001].
15 11
16 12 26. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: validity of a new measure for
17 13 evaluating the severity of somatic symptoms. *Psychosom Med* 2002;64(2):258-266.
18 14 doi:10.1097/00006842-200203000-00008.
19 15
20 16 27. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized
21 17 anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166(10):1092-1097.
22 18 doi:10.1001/archinte.166.10.1092.
23 19
24 20 28. Nieuwenhuijsen K, Noordik E, van Dijk FJH, et al. Return to work perceptions and actual
25 21 return to work in workers with common mental disorders. *J Occup Rehabil*. 2013;23(2):290–9.
26 22 doi:10.1007/s10926-012-9389-6 [published Online First: 3 November 2012].
27 23
28 24 29. van Oostrom SH, Mechelen van MW, Terluin B, et al. A workplace intervention for sick-
29 25 listed employees with distress: results of a randomised controlled trial. *Occup*
30 26 *Environ Med* 2010;67(9):596–602. doi:10.1136/oem.2009.050849 [published Online First: 2
31 27 April 2010].
32 28
33 29 30. Volker D, Zijlstra-Vlasveld MC, Brouwers EPM, et al. Return-to-work self-efficacy and
34 30 actual return to work among long-term sick-listed employees. *J Occup Rehabil* 2015; 25
35 31 (2):423-341. doi:10.1007/s10926-014-9552-3 [published Online First: 30 October 2014].
36 32
37 33 31. Hakkaart-van Roijen L. Manual Trimbos/iMTA questionnaire for costs associated with
38 34 psychiatric illness (in Dutch). Rotterdam: Institute for Medical Technology Assessment 2002.
39 35
40 36 32. Euroqol Group. *Eq-5D User Guide*. Rotterdam, The Netherlands: Sanders Instituut, EUR
41 37 1995.
42 38
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 1 33. Lamers, L. M., McDonnell, J., Stalmeier, P. F. M., Krabbe, P. F. M., & Busschbach, J. J. V.
4 2 (2006). The Dutch tariff: results and arguments for an effective design for national EQ-5D
5 3 valuation studies. *Health Econ*, 15(10), 1121-32. doi:10.1002/hec.1124 [published Online
6 4 First: 19 June 2006].
7 5
8
9
10 6 34. Hakkaart L, Tan S, Bouwmans C. Manual for cost research. Methods and standard costs for
11 7 economic evaluations in healthcare (in Dutch). Rotterdam: Institute for Medical Technology
12 8 Assessment, Erasmus University Rotterdam 2010.
13 9
14
15
16 10 35. Zorginstituut Nederland (2014a). Dutch Health Care Insurance Board (in Dutch)
17 11 (<http://www.medicijnkosten.nl/>). Accessed 7 May 2014.
18 12
19
20 13 36. Zwaap J, Knies S, van der Meijden C, et al. Kosteneffectiviteit in de praktijk. Diemen:
21 14 Zorginstituut Nederland 2015.
22 15
23
24
25 16 37. Rice DP, Cooper BS. The economic value of human life. *Am J Public Health Nations Health*
26 17 1967;57:1954–1966. doi: 10.2105/AJPH.57.11.1954.
27 18
28
29 19 38. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for
30 20 reporting parallel group randomised trials. *BMJ* 2010;340:c332. doi:10.1136/bmj.c332.
31 21
32
33 22 39. Campbell MK, Piaggio G, Elbourne DR, et al. Consort 2010 statement: extension to cluster
34 23 randomised trials. *BMJ* 2012;345:e5661. doi:10.1136/bmj.e5661.
35 24
36
37
38 25 40. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation
39 26 Reporting Standards (CHEERS) statement. *BJOG* 2013;120:765-770. doi:10.1136/bmj.f1049.
40 27
41
42 28 41. Schene AH, Koeter MW, Kikkert MJ, et al. Adjuvant occupational therapy for work-related
43 29 major depression works: randomized trial including economic evaluation. *Psychol*
44 30 *Med* 2007;37:351–362. doi:dx.doi.org/10.1017/S0033291706009366 [published Online First:
45 31 20 November 2006].
46 32
47
48
49
50 33 42. Lerner D, Adler D, Hermann RC, et al: Impact of a work-focused intervention on the
51 34 productivity and symptoms of employees with depression. *J Occup Environ Med* 54:128–135,
52 35 2012. doi:10.1097/JOM.0b013e31824409d8 [published Online First: 1 March 2015].
53 36
54
55
56 37 43. Arends I, Bültmann U, van Rhenen W, et al. Economic evaluation of a problem solving
57 38 intervention to prevent recurrent sickness absence in workers with common mental disorders.
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

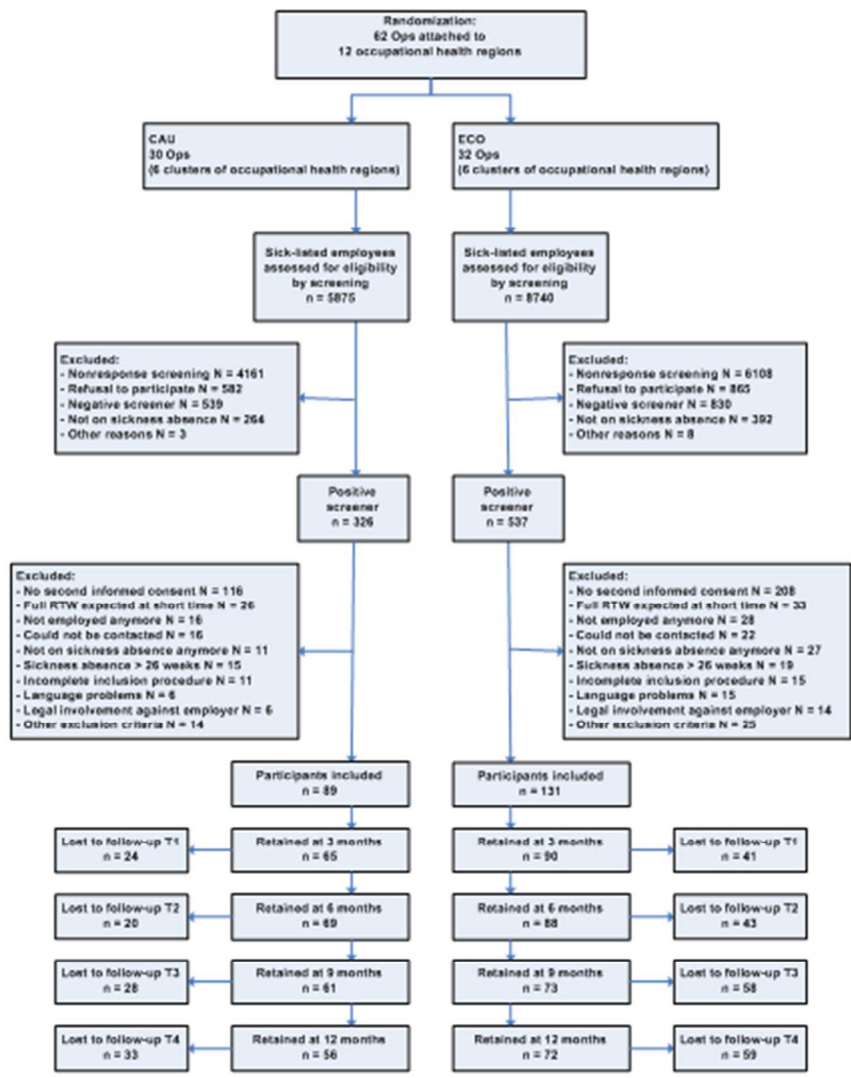
1 *PLoS One* 2013;8:e71937. doi:10.1371/journal.pone.0071937 [published Online First: 12
2 August 2013].

3
4
5
6
7
8 44. Noben C, Evers S, Nieuwenhuijsen K, et al. Protecting and promoting mental health of
9 nurses in the hospital setting: is it cost-effective form an employer’s perspective?
10 *Int J Occup Med Environ Health* 2015;28(5). doi:10.13075/ijomeh.1896.00465.

11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

8 45. Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from
9 disease and injury: disability weights measurement study for the Global Burden of Disease
10 Study 2010. *Lancet*. 2012;380:2129–43. doi:10.1016/S0140-6736(12)61680-8.

For peer review only



Flowchart of the participants



Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

| Section/Topic | Item No | Standard Checklist item | Extension for cluster designs | Page No * |
|----------------------------------|---------|--|---|-----------|
| Title and abstract | | | | |
| | 1a | Identification as a randomised trial in the title | Identification as a cluster randomised trial in the title | 3 |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) ^{1,2} | See table 2 | 3 |
| Introduction | | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | Rationale for using a cluster design | 4,5 |
| | 2b | Specific objectives or hypotheses | Whether objectives pertain to the cluster level, the individual participant level or both | 5 |
| Methods | | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | Definition of cluster and description of how the design features apply to the clusters | 5 |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | | N/A |
| Participants | 4a | Eligibility criteria for participants | Eligibility criteria for clusters | 6 |
| | 4b | Settings and locations where the data were collected | | 6 |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | Whether interventions pertain to the cluster level, the individual participant level or both | 7 |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and | Whether outcome measures pertain to the cluster level, the individual participant level or both | 7/8 |

| | | | | |
|---|-----|---|---|-----|
| | | when they were assessed | | |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | | N/A |
| Sample size | 7a | How sample size was determined | Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or <i>k</i>), and an indication of its uncertainty | N/A |
| | 7b | When applicable, explanation of any interim analyses and stopping guidelines | | N/A |
| Randomisation: | | | | |
| Sequence generation | 8a | Method used to generate the random allocation sequence | | 6 |
| | 8b | Type of randomisation; details of any restriction (such as blocking and block size) | Details of stratification or matching if used | 5/6 |
| Allocation concealment mechanism | 9 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both | 5/6 |
| Implementation | 10 | Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions | Replace by 10a, 10b and 10c | 6 |
| | 10a | | Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions | |
| | 10b | | Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete | |

| | | | | |
|---|-----|--|---|---------|
| | | | enumeration, random sampling) | |
| | 10c | | From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation | |
| Blinding | 11a | If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how | | 6 |
| | 11b | If relevant, description of the similarity of interventions | | N/A |
| Statistical methods | 12a | Statistical methods used to compare groups for primary and secondary outcomes | How clustering was taken into account | 9/10 |
| | 12b | Methods for additional analyses, such as subgroup analyses and adjusted analyses | | 10 |
| Results | | | | |
| Participant flow (a diagram is strongly recommended) | 13a | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome | 6/10/11 |
| | 13b | For each group, losses and exclusions after randomisation, together with reasons | For each group, losses and exclusions for both clusters and individual cluster members | 10/11 |
| Recruitment | 14a | Dates defining the periods of recruitment and follow-up | | 6 |
| | 14b | Why the trial ended or was stopped | | N/A |
| Baseline data | 15 | A table showing baseline demographic and clinical | Baseline characteristics for the individual and cluster levels as | Table 1 |

| | | characteristics for each group | applicable for each group | |
|--------------------------------|-----|---|--|-------|
| Numbers analysed | 16 | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | For each group, number of clusters included in each analysis | 6/9 |
| Outcomes and estimation | 17a | For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval) | Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome | 11-15 |
| | 17b | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | | N/A |
| Ancillary analyses | 18 | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | | 14/15 |
| Harms | 19 | All important harms or unintended effects in each group (for specific guidance see CONSORT for harms ³) | | N/A |
| Discussion | | | | |
| Limitations | 20 | Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses | | 16/17 |
| Generalisability | 21 | Generalisability (external validity, applicability) of the trial findings | Generalisability to clusters and/or individual participants (as relevant) | 17 |
| Interpretation | 22 | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | | 17-19 |
| Other information | | | | |
| Registration | 23 | Registration number and | | 5/6 |

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

| | | |
|-----------------|----|---|
| | | name of trial registry |
| Protocol | 24 | Where the full trial protocol can be accessed, if available |
| Funding | 25 | Sources of funding and other support (such as supply of drugs), role of funders |

** Note: page numbers optional depending on journal requirements*

For peer review only

Table 2: Extension of CONSORT for abstracts^{1,2} to reports of cluster randomised trials

| Item | Standard Checklist item | Extension for cluster trials |
|---------------------------|---|--|
| Title | Identification of study as randomised | Identification of study as cluster randomised |
| Trial design | Description of the trial design (e.g. parallel, cluster, non-inferiority) | |
| Methods | | |
| Participants | Eligibility criteria for participants and the settings where the data were collected | Eligibility criteria for clusters |
| Interventions | Interventions intended for each group | |
| Objective | Specific objective or hypothesis | Whether objective or hypothesis pertains to the cluster level, the individual participant level or both |
| Outcome | Clearly defined primary outcome for this report | Whether the primary outcome pertains to the cluster level, the individual participant level or both |
| Randomization | How participants were allocated to interventions | How clusters were allocated to interventions |
| Blinding (masking) | Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment | |
| Results | | |
| Numbers randomized | Number of participants randomized to each group | Number of clusters randomized to each group |
| Recruitment | Trial status ¹ | |
| Numbers analysed | Number of participants analysed in each group | Number of clusters analysed in each group |
| Outcome | For the primary outcome, a result for each group and the estimated effect size and its precision | Results at the cluster or individual participant level as applicable for each primary outcome |
| Harms | Important adverse events or side effects | |
| Conclusions | General interpretation of the results | |
| Trial registration | Registration number and name of trial register | |
| Funding | Source of funding | |

¹ Relevant to Conference Abstracts

REFERENCES

- 1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283
- 2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20
- 3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

| Section/item | Item No | Recommendation | Reported on page No/line No |
|---------------------------------|---------|--|-----------------------------|
| Title and abstract | | | |
| Title | 1 | Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared. | 3 |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | 3 |
| Introduction | | | |
| Background and objectives | 3 | Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions. | 4,5 |
| Methods | | | |
| Target population and subgroups | 4 | Describe characteristics of the base case population and subgroups analysed, including why they were chosen. | 6 |
| Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | 6 |
| Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | 9 |
| Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen. | 7 |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | 8 |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | 8 |
| Choice of health outcomes | 10 | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed. | 8/9 |
| Measurement of effectiveness | 11a | <i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. | 5-7 |



| | | | | |
|----|-------------------------|-----|---|-------|
| 1 | | 11b | <i>Synthesis-based estimates:</i> Describe fully the methods used for | |
| 2 | | | identification of included studies and synthesis of clinical | |
| 3 | | | effectiveness data. | N.A. |
| 4 | | | | |
| 5 | Measurement and | 12 | If applicable, describe the population and methods used to | |
| 6 | valuation of preference | | elicit preferences for outcomes. | |
| 7 | based outcomes | | | N.A. |
| 8 | | | | |
| 9 | Estimating resources | 13a | <i>Single study-based economic evaluation:</i> Describe approaches | |
| 10 | and costs | | used to estimate resource use associated with the alternative | |
| 11 | | | interventions. Describe primary or secondary research methods | |
| 12 | | | for valuing each resource item in terms of its unit cost. | |
| 13 | | | Describe any adjustments made to approximate to opportunity | |
| 14 | | | costs. | 7,8 |
| 15 | | | | |
| 16 | | 13b | <i>Model-based economic evaluation:</i> Describe approaches and | |
| 17 | | | data sources used to estimate resource use associated with | |
| 18 | | | model health states. Describe primary or secondary research | |
| 19 | | | methods for valuing each resource item in terms of its unit | |
| 20 | | | cost. Describe any adjustments made to approximate to | |
| 21 | | | opportunity costs. | N.A. |
| 22 | | | | |
| 23 | Currency, price date, | 14 | Report the dates of the estimated resource quantities and unit | |
| 24 | and conversion | | costs. Describe methods for adjusting estimated unit costs to | |
| 25 | | | the year of reported costs if necessary. Describe methods for | |
| 26 | | | converting costs into a common currency base and the | |
| 27 | | | exchange rate. | 8 |
| 28 | | | | |
| 29 | Choice of model | 15 | Describe and give reasons for the specific type of decision- | |
| 30 | | | analytical model used. Providing a figure to show model | |
| 31 | | | structure is strongly recommended. | N.A. |
| 32 | | | | |
| 33 | Assumptions | 16 | Describe all structural or other assumptions underpinning the | |
| 34 | | | decision-analytical model. | N.A. |
| 35 | | | | |
| 36 | Analytical methods | 17 | Describe all analytical methods supporting the evaluation. This | |
| 37 | | | could include methods for dealing with skewed, missing, or | |
| 38 | | | censored data; extrapolation methods; methods for pooling | |
| 39 | | | data; approaches to validate or make adjustments (such as half | |
| 40 | | | cycle corrections) to a model; and methods for handling | |
| 41 | | | population heterogeneity and uncertainty. | 9,10 |
| 42 | | | | |
| 43 | Results | | | |
| 44 | Study parameters | 18 | Report the values, ranges, references, and, if used, probability | |
| 45 | | | distributions for all parameters. Report reasons or sources for | |
| 46 | | | distributions used to represent uncertainty where appropriate. | |
| 47 | | | Providing a table to show the input values is strongly | |
| 48 | | | recommended. | 10-15 |
| 49 | | | | |
| 50 | Incremental costs and | 19 | For each intervention, report mean values for the main | |
| 51 | outcomes | | categories of estimated costs and outcomes of interest, as well | |
| 52 | | | as mean differences between the comparator groups. If | |
| 53 | | | applicable, report incremental cost-effectiveness ratios. | 10-15 |
| 54 | | | | |
| 55 | Characterising | 20a | <i>Single study-based economic evaluation:</i> Describe the effects | |
| 56 | uncertainty | | of sampling uncertainty for the estimated incremental cost and | |
| 57 | | | incremental effectiveness parameters, together with the impact | 12-14 |
| 58 | | | | |
| 59 | | | | |
| 60 | | | | |

| | | | |
|--|-----|--|-------|
| | | of methodological assumptions (such as discount rate, study perspective). | |
| | 20b | <i>Model-based economic evaluation</i> : Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | N.A. |
| Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | N.A. |
| Discussion | | | |
| Study findings, limitations, generalisability, and current knowledge | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | 15-19 |
| Other | | | |
| Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | 19 |
| Conflicts of interest | 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations. | 19 |

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

The citation for the CHEERS Task Force Report is:
 Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. *Value Health* 2013;16:231-50.