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Title Page

Full title:

Cost-effectiveness of an Internet-based perioperative care programme to enhance postoperative recovery in gynaecological patients: economic evaluation alongside a stepped-wedge cluster-randomised trial

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Abstract

Objectives To evaluate the cost-effectiveness and cost-utility of an Internet-based perioperative care programme compared with usual care for gynaecological patients.

Design Economic evaluation from a societal perspective alongside a stepped-wedge cluster-randomised controlled trial with 12 months follow-up.

Setting Secondary care, nine hospitals in the Netherlands, 2011-2014.

Participants 433 employed women aged 18-65 scheduled for a hysterectomy and/or laparoscopic adnexal surgery.

Intervention An Internet-based care programme aimed at improving convalescence and preventing delayed return to work following gynaecological surgery was sequentially rolled out. Depending on the implementation phase of their hospital, patients were allocated to usual care (n=206) or the care programme (n=227).

Main outcome measures The primary outcome was duration until full sustainable return to work (RTW). Secondary outcomes were quality adjusted life years (QALYs), health-health-related quality of life and recovery.

Results At 12 months, there were no statistically significant differences in total societal costs (€-647; 95% CI €-2116 to €753) and duration until RTW (-4.1; 95% CI -10.8 to 2.6) between groups. The incremental cost-effectiveness ratio (ICER) for RTW was 56; each day earlier RTW in the intervention group was associated with cost savings of 56 euros compared to usual care. The probability of the intervention being cost-effective was 0.79 at a willingness-to-pay (WTP) of €0 per day earlier RTW, which increased to 0.97 at a WTP of €76 per day earlier RTW. The difference in QALYs gained over 12 months between the groups was clinically irrelevant resulting in a low probability of cost-effectiveness for QALYs.

Conclusions The care programme is considered cost-effective in comparison with usual care for duration until sustainable RTW after gynaecological surgery for benign disease. Future research should indicate whether widespread implementation of this care programme has the potential to reduce societal costs associated with gynaecological surgery.

Trial registration Netherlands National Trial Register NTR2933.

Key words gynaecology; Internet; telemedicine; self-management; convalescence; return to work; economic evaluation.

Strengths and limitations of this study

- This is the first economic evaluation on an Internet-based care programme aimed at improving convalescence and preventing delayed return to work following gynaecological surgery.
- The study was conducted alongside a cluster-randomised controlled trial allowing prospective collection of relevant cost and effect data.
- The study was performed from a societal perspective and costs associated with lost productivity included both absenteeism as well as presenteeism costs.
- A latent barrier to future acceptance and implementation of the care programme lies in the fact that the costs and benefits of the care programme are separated between different types of stakeholders.

Main document

Introduction

At present, there is a transition of perioperative care from the hospital setting towards the home environment.[1-4] The introduction of advanced surgical techniques in combination with the implementation of "fast-track" clinical pathways have considerably reduced the length of postoperative hospital stays and many (complex) surgeries are now being performed in an ambulatory setting.[5-7] This is beneficial from the perspective of the healthcare system, as it leads to the containment of healthcare costs.[1, 8]

However, costs associated with lost productivity following surgery contribute to the total societal costs of surgical procedures as well, and are mostly not taken into account. Moreover, there is considerable evidence that the duration of sick leave following gynaecological surgery generally exceeds the period considered appropriate by specialists.[9] Therefore, preventing unnecessary prolonged recovery following gynaecological surgery, may translate into considerable savings for society.

We developed an Internet-based care programme for patients undergoing gynaecological surgery for benign disease, aimed at facilitating recovery after discharge and preventing delayed return to work.[10, 11] In this paper, we report on the cost-effectiveness and cost-utility of the Internet-based care programme compared to usual care. The findings on clinical effectiveness were reported in a separate paper.

Methods

Study design and participants

This economic evaluation was performed from a societal perspective and was carried out alongside a stepped-wedge cluster randomised controlled trial comparing an Internet-based care programme with usual care for patients undergoing benign gynaecological surgery. The study was done in the Netherlands between April 2011 and July 2014.The follow-up period was 12 months. The trial protocol has been published previously in accordance to CONSORT extended guidelines.[9]

The clusters in this trial were formed by separate hospitals. A total of nine hospitals participated, which were selected before the start of the trial. Hospitals were eligible if they

performed at least 100 hysterectomies or laparoscopic adnexal surgeries annually, and were located within 50km of the VU medical centre, Amsterdam, the Netherlands.

Patients were recruited from the waiting lists for hysterectomy (abdominal, vaginal or laparoscopic) and laparoscopic adnexal surgery. Eligible participants were women aged 18-65 who were employed for at least eight hours a week (unpaid or paid employment, or self-employed). We excluded patients who had severe benign comorbidity, had a malignancy, were pregnant, were computer or Internet illiterate, were involved in a lawsuit against their employer, were on disability sick leave before surgery, or had insufficient command of Dutch.

Randomisation and blinding

Randomization took place at the level of the clusters and determined the order in which the intervention was implemented in the participating hospitals. The sequence was generated by a statistician using a computer generated list of random numbers. A stepped wedge approach was employed as it enabled us to study the implementation process as well.[9]

Patients, clinicians and researchers could not be blinded for the intervention. However, group allocation was concealed until patients had agreed to participate and provided written informed consent. Data analysts (EB, JB) were masked to group allocation.

Intervention care programme and implementation strategy

The development and content of the intervention care programme have been described elsewhere in more detail.[9, 11] A multi-faceted implementation strategy was employed to achieve maximal adoption of the care programme, targeting three different levels.

At the level of the organization, the structure of healthcare was changed by the introduction of the interactive web portal that was accessible for patients as well as their healthcare professionals. In addition, care managers were trained to help patients identify possible barriers to resuming work activities and could assist, if necessary, in the planning and execution of work resumption, before and after surgery.

At the level of the healthcare professional, educational training sessions were organised to introduce an earlier developed guideline on postoperative convalescence recommendations to stimulate evidence-based patient education.[10]

At the patient level, the care programme consisted of two steps. First, all participants allocated to the intervention group received access to the web portal several weeks prior to their surgery (eHealth intervention). The interactive web portal facilitated self-management by providing patients with individual tailored convalescence recommendations throughout the entire surgical pathway as well as monitoring recovery postoperatively through an interactive self-assessment tool. Second, for those patients at risk of prolonged sick leave, a care manager was available to provide additional guidance in the process of resuming work activities (occupational intervention).

Usual Care

Before the care programme was implemented in the hospitals, participating patients received usual care. Although considerable variation in usual care exists in the Netherlands, postoperative patients generally receive verbal instructions at discharge by a nurse and/or physician, sometimes accompanied by a letter or brochure. Usually, a postoperative consultation is planned six weeks after surgery. Due to Dutch legislation, employed patients who do not resume work within 6 weeks after the surgery are invited for a consultation with their occupational physician.

Main outcome measures

The primary outcome was duration until sustainable return to work (RTW) defined as the resumption of own work or other work with equal earnings, for at least 4 weeks without (partial or full) recurrence of sick leave.[12] Data on return to work were collected by means of monthly electronic sick leave calendars.

Quality adjusted life years (QALYs) was one of the secondary outcomes and was measured using the Dutch version of the EuroQol five-dimensional questionnaire (EQ-5D-3L).[13] The Dutch tariff was used to estimate the utility of EQ-5D-3L health states.[14] QALYs were calculated by multiplying the utility with the amount of time a patient spent in a particular health state. Transitions between health states were linearly interpolated. Other secondary outcomes included health-related quality of life assessed by Short-Form Health Survey (SF-36)[15], and recovery assessed by the Recovery Index (RI-10).[16] All secondary outcomes were assessed at baseline, and at 2, 6, 12, 26, and 52 weeks follow-up.

Service use and costs

The intervention and implementation strategy costs consisted of costs related to implementing the new care programme. A bottom-up micro-costing approach was used for estimating intervention costs, using detailed data regarding the quantity and unit prices of: (1) the training sessions of involved healthcare professionals (clinical staff, occupational physicians, occupational therapist), (2) the eHealth intervention (hosting of web portal, administrator time), and (3) the occupational intervention (number and duration of consultations).[17]

Data on healthcare services used and support received by the participants were collected using electronic questionnaires during one year. Each month, the patient was asked to report service use over the previous month. Patients who were not sick listed and did not have any healthcare costs during three consecutive months, received a shortened version of the questionnaire. In case of no response, electronic reminders were sent after one and two weeks. If participants did not respond to the electronic reminders either, an additional attempt was made to complete the missing data per email, mail or telephone every three months.

Only healthcare utilization and support related to the gynaecological surgery were collected, and included the following categories: surgery and initial hospitalization, primary and secondary care including complementary medicine, medication and medical aids, home care and informal help.

Service utilization was valued using Dutch standard costs.[18] If these were unavailable, prices according to professional organizations were used. The prices of prescribed drugs were estimated using the prices of the Royal Dutch Society for Pharmacy.[19]

Productivity Loss

Absenteeism costs were calculated using the Human Capital Approach (HCA). The net number of sick leave days during follow-up were multiplied by the estimated costs of one day of sick leave for females, stratified for age.[18] In case of partial sick leave, we assumed that participants were 100% productive during the hours of partial work resumption.

Presenteeism (i.e. reduced productivity while at work) was assessed monthly after full resumption of work using two items of the "Productivity and Disease Questionnaire" (PRODISQ).[20] Patients were asked to report the quantity (q1) and quality (q2) of the work

performed during the latest day at work on an 11-point scale, ranging from "nothing/very bad quality" (0) to "same as normal"(10).

The level of presenteeism ($Pres_{day}$) on the latest day at work was calculated using the following formula: $Pres_{day} = (1-((q1*q2)/100))$. Assuming linearity, the level of presenteeism on the latest day at work was then extrapolated over the total month. The total number of workdays lost due to presenteeism were calculated ($Pres_{month}$) by multiplying the participants' presenteeism level by their number of days worked during that month. Subsequently, presenteeism costs per month were calculated by multiplying $Pres_{month}$, by the estimated costs of one day of lost productivity.

The index year of the study was 2014. Discounting of costs was not necessary because the follow-up was one year.[21]

Statistical analysis

The sample size of the study (n=454) was calculated for detecting a relevant difference in return to work (hazard ratio (HR) of 1.5) in the main outcome study.[9] The economic evaluation was done according to the intention to treat principle. Missing cost and effect data during follow-up were imputed using multiple imputation by chained equations (MICE). Multiple imputation was done using SPSS 16.0 with predictive mean matching. An imputation model containing demographic and prognostic variables was used to create five complete datasets after which the loss of efficiency was smaller than 5%.[22] Rubin's rules were used to pool effects and costs from the five imputed datasets.[23]

Differences in costs and effects were estimated using linear multilevel regression analyses, while adjusting for type of surgery. Clustering at the hospital- and patient-level was accounted for in these multilevel models. For the cost-effectiveness and cost-utility analyses, we calculated incremental cost-effectiveness ratios (ICERs) by dividing the incremental costs by the incremental effects. The ICER indicates the additional investments needed for the intervention to gain one extra unit of effect compared with usual care. In the ICER for duration until RTW, productivity costs due to sick leave were excluded from the cost estimates to avoid double counting.

We used non-parametric bootstrapping with 5000 replications to estimate 95% confidence intervals around cost differences and the uncertainty surrounding the ICERs.[24] To account for the clustering of data, bootstrap replications were stratified for hospital.[25] Bootstrapped cost-effect pairs were plotted on cost-effectiveness planes (CE planes) and used to estimate cost-effectiveness acceptability curves (CEA curves). CEA curves show the probability that a treatment is cost effective in comparison with the control treatment at a specific ceiling ratio, which is the amount of money society is willing to pay to gain one extra unit of effect.

Sensitivity analyses

To assess whether protocol deviations influenced the treatment effect, a per-protocol analysis was performed. In addition, to assess the robustness of the results, we carried out three sensitivity analyses. Firstly, we did a complete-case analysis to assess the cost-effectiveness of the interventions excluding patients who were lost to follow-up. Secondly, we replicated the cost-effectiveness analysis using the Friction Cost Approach. The FCA assumes that costs are limited to the friction period (i.e. the period needed to replace a sick worker). A friction period of 23 weeks and an elasticity of 0.8 was used. Thirdly, an analysis from the healthcare perspective was performed including only healthcare costs.

All statistical analyses followed a predefined analysis plan and were done in SPSS (version 16.0) and STATA (version 12SE).

Results

Participants

During the study period, 1591 patients were scheduled for a hysterectomy and/or laparoscopic adnexal surgery in the participating hospitals. In total, 433 patients enrolled in the study, 206 patients during the control phase and 227 patients during intervention phase (figure 1).

Participants' demographic and prognostic variables are presented in table 1. Complete follow-up data were obtained from 92.6% of the participants on the primary outcome RTW, from 71.8% on the secondary outcomes, and 70.0% on healthcare utilization. Baseline characteristics did not differ between participants with and without complete cost data, except that patients with complete data on healthcare utilization used the Internet more frequently than women with incomplete data.

Service use and costs

Table 2 presents the costs of self-reported service use per category over the 12 months of follow-up stratified by treatment group and the mean cost differences between both groups.

Intervention costs were €80 per participant (online supplementary table S1). Total societal costs per patient were €12,266 in the intervention group and €13,795 in the usual care group. After correction for clustering by hospital and adjustment for surgery type, total societal costs in the intervention group were €647 lower compared to the usual care group, but this difference was not statistically significant (95% CI €-2116 to €753). In both groups, costs related to productivity losses were about two times higher than total healthcare costs. Both healthcare costs and lost productivity costs were lower in the in the intervention group compared to the usual care group, however, these differences were not statistically significant. Only costs for secondary care were significantly lower in the intervention group compared to the usual care group (€242 and €458, respectively).

Effectiveness

The mean duration until RTW in the intervention group was 49.6 days versus 56.2 days in the usual care group. The adjusted difference in duration until RTW between intervention and usual care was -4.1 days (95% CI -10.8 to 2.6) (table 3). For the other outcomes, no statistically differences were found between both groups at 12 months either.

Cost-effectiveness

The results of the cost-effectiveness analysis for duration until RTW are presented in table 4. The incremental cost-effectiveness ratio (ICER) for sustainable RTW was 56 indicating that each day earlier RTW in the intervention group is associated with cost savings of 56 euros in comparison with the usual care group. In the cost-effectiveness plane, 69% of the incremental cost effect pairs were located in the south east quadrant indicating that the intervention is more effective and less costly than usual care (figure 2a). The cost-effectiveness acceptability curve presented in figure 2b shows that if the societal willingness-to-pay (WTP) for one earlier day of RTW is €0, the probability that the intervention is cost-effective in comparison with usual care is 0.79. This probability increases to 0.97 at max if the WTP is €76 per day earlier RTW.

As the differences observed for the outcomes health-related quality of life and recovery after 12 months were small and not significant, the ICERs for these outcomes were quite large. In

the cost-effectiveness planes, the majority of cost-effect pairs were located in the southern quadrants, indicating the intervention was less expensive. However, the cost-effect pairs were roughly divided between the eastern and western quadrant indicating that the intervention can lead to both better and worse outcomes compared to usual care.

Cost-utility

The difference in QALYs gained over 12 months between the two study groups was small and not statistically significant or clinically relevant (table 4). Therefore, the ICER for QALYs became extraordinary large (half million Euros). As a result, the probability that the intervention was cost-effective in comparison with usual care was considerably lower than for the primary outcome (0.77 at WTP is €0 per QALY gained and decreasing at higher WTP values).

Per-protocol analysis

In the per-protocol analysis 40 patients were excluded because they did not receive the care according to protocol due to several reasons: did not fit the inclusion criteria (n=3); had a more severe surgery than planned (n=25), or had a complicated postoperative course and needed a repeat surgery during follow-up (n=12). By excluding those patients, the difference in effect became larger, but was still not significant (-6.4 days, 95% CI -12.9 to 0.20) and the cost differences became statistically significant in favour of the intervention (mean difference €-359, 95% CI -866 to -11) (table 5). Hence, compared to the main analysis, the probability of cost-effectiveness increased considerably at a WTP of €0 per one day earlier RTW (from 0.79 to 0.92).

Sensitivity analyses

The results of the primary outcome in the sensitivity analyses differed in some aspects from the main analysis (table 5). First, in the complete-case analysis, the effect difference between study groups became larger in favour of the intervention group, but the cost savings in the intervention group as compared to usual care became smaller. The probability of cost-effectiveness compared to the main analysis therefore decreased (from 0.79 to 0.55). Second, in the analyses performed from the healthcare perspective, cost savings became much smaller, as costs associated with lost productivity were not taken into account. As a result the probability of cost-effectiveness reduced (from 0.79 to 0.61). Finally, the results from the

friction cost analysis were identical to the intention to treat analysis, indicating that the majority of patients returned to their work before the end of the friction period of 23 weeks.

The results of the per-protocol analyses and sensitivity analyses for the secondary outcomes QALYs, health-related quality of life and recovery are presented in online supplementary table S2. In the per-protocol analyses, cost differences became larger in favour of the intervention group, however, they did not reach statistical significance. The probability of cost-effectiveness at a WTP of €0 per unit of effect increased from 0.77 to 0.93. In contrast to the complete-case analysis for the primary outcome, the complete-case analyses for the secondary outcomes showed a statistical significant increase in cost savings in the intervention group. The probability of cost-effectiveness at a WTP of €0 per unit of effect increased from 0.77 to 0.98

Discussion

In this study, we evaluated the cost-effectiveness and cost-utility of a rigorously designed Internet-based perioperative care programme compared with usual care for gynaecological patients. Our results show that for the primary outcome duration until full resumption of work, the probability that the care programme is cost-effective is substantial: 0.79 at a willingness to pay of €0 per day earlier RTW, which increases to 0.97 at a willingness to pay of €76 per day earlier RTW.

Interpretation of the findings

In the current economic evaluation, the adjusted mean difference until RTW between study groups was not statistical significant (-4.1 days, 95% CI -10.8 to 2.6). Due to the skewness of RTW-data, presenting the median difference is more appropriate, however, this is not possible in economic evaluations. We hypothesise that this may have caused the difference in duration until RTW between study groups being statistical non-significant, while in fact, the difference might be of clinical relevance.

In addition, the cost-difference between the intervention group and the control group was not statistically significant either, although total societal costs were lower in the intervention group than in the control group. A possible explanation might be that the sample size of this study was based on the primary outcome full sustainable return to work, and, therefore,

underpowered to detect relevant cost differences, as cost data are right skewed and require relative large samples.[26]

Secondary care costs in the intervention group were significantly lower compared to the usual care group. The underlying mechanism should be investigated further, as it might indicate that patients receiving additional perioperative care were more confident in their own self-management skills preventing them from visiting a healthcare professional. In addition, costs associated with primary care were similar in both groups, demonstrating that the care programme did not cause a shift from secondary care to primary care in the intervention group compared to the usual care group. Concerns of increased workload in the primary care setting due to changes in perioperative care have been reported before, however, seem to be ungrounded.[27, 28]

We did not find any clinical relevant differences in the secondary outcomes. Thus, despite the possible difference in the RTW rates between study groups, this did not have an effect on patients' perceptions about their quality of life and recovery. Possibly, the surgery itself has a much larger impact on these outcomes than the method of postoperative guidance.

The results of the per-protocol analyses, were slightly more favourable than those of the main analyses. Thus, by presenting the care programme to the ideal target population, the probability of cost-effectiveness of the care programme in comparison with usual care increases. This is in concordance with our initial objective to develop Internet-based care programme for women undergoing an uncomplicated surgical procedure.[10] It may be challenging to identify future patients who will benefit most from the care programme, as complications cannot always be predicted pre-operatively. In addition, it should be investigated further what the needs are of patients with a complicated course and how they should best be guided and monitored during their recovery.

Strengths and weaknesses of the study

Several strengths of the present study are noteworthy. First of all, we are not aware of other current perioperative interventions that aim at preventing unnecessary prolonged recovery and reducing sick leave in order to contain societal costs associated with gynaecological surgical care. Second, analyses were performed alongside a pragmatic trial, allowing prospective collection of relevant cost and effect data and enabling the evaluation of the intervention's

cost-effectiveness under real world conditions.[26] The third strength concerns the use of linear multilevel analyses to account for possible clustering of data as a result of the chosen study design. Randomization at cluster level was chosen to prevent contamination between the study arms. Moreover, the employment of a stepped wedge design allowed the sequential implementation of the care programme in the participating hospitals, providing the possibility to study the implementation process as well.

Our study also has limitations. The first limitation is the collection of cost data through self-reported retrospective questionnaires. However, since administrative data on service use are very hard to obtain in the Netherlands, societal cost data can only be collected by means of self-report. In order to prevent recall-bias, we minimised the recall period to only one month. In addition, if there was recall bias, it seems unlikely that this systematically differed between the study groups. Therefore, we expect that this does not affect our estimations. A second limitation concerns the amount of incomplete data. Despite our efforts to obtain full data from the patients in the trial, only 70.4% of the study population had complete cost data. Although this is an acceptable rate of missing data, complete-case analyses may be biased and have less precision.[29, 30] We tried to account for this by applying multiple imputation for missing data.[31] Comparison of participants with complete and incomplete data resulted in a number of variables that predicted the presence of missing data. Therefore, we concluded that the data was missing at random, making multiple imputation the appropriate method to deal with the missing data.

Comparison with other studies

We showed that costs associated with productivity loss following gynaecological surgery were about two times higher than healthcare costs. We are not aware of previously published literature in the gynaecological field in which this was demonstrated before. As a matter of fact, outcomes such as long-term convalescence, return to normal activities and absenteeism following gynaecological surgery are under-reported in clinical trials. In a review of Roumm et. al. assessing the clinical and economic benefits of minimal invasive surgery compared to open alternatives, only five of the 19 eligible studies reported data on return to work or return to normal activities, while 15 studies reported on hospital costs and all studies reported on length of stay.[32] Similarly, in a recent Cochrane systematic review assessing the effectiveness and safety of different surgical approaches to hysterectomy in women with benign

gynaecological disease, 45 of the 47 included studies reported on the length of postoperative hospital stay and only 19 studies reported data on return to normal activities.[33]

Cost-effectiveness is one of the most frequently cited reason for developing Internet interventions, because of the relative low delivery costs and the potential high impact.[34] However, economic evaluations are mainly lacking. A recent systematic review that evaluated the effect of perioperative e-Health interventions on the postoperative course, concluded that only 6 of 19 included studies reported on costs and in only one study a full economic evaluation was performed.[35] Thus, the current study addresses this literature gap as well.

Policy implications and recommendations

Whether the perioperative Internet-based care programme under study is considered cost-effective in comparison with usual care in accelerating return to work following gynaecological surgery depends on society's willingness to pay for a reduced sick leave day, as well as the probability of cost-effectiveness that is considered acceptable. Our results show that the probability of cost-effectiveness is 0.97 at a WTP of €76 per day earlier RTW. Considering that on average the costs of a day of sickness absence are €230,[18] we expect that this intervention can be considered cost-effective in comparison with usual care.

A latent barrier to future acceptance and implementation of the care programme lies in the fact that the costs and benefits of the care programme are separated between different types of stakeholders. In the Netherlands, medical costs are paid by the government and health insurance companies and sickness benefits are the main responsibility of the employers, which makes the shifting of costs across these sectors hard. As follows, investments are made in the healthcare sector for implementing the care programme and changing care processes, while the largest benefits accrue to employers through reduced lost productivity costs. However, many countries have an employer-provided health insurance (e.g. the United States), and in those countries this Internet-based care programme is much more likely to be adapted as investments in the Internet-based care programme may directly lead to savings through improved productivity rates.

Conclusions

The encouraging outcomes of this trial show that there is an economic case for supporting patients in the perioperative period with an Internet-based care programme. The care

programme has a potential to lead to societal cost savings as a result of a reduction in the duration until full sustainable RTW. If society is willing to pay €76 per day earlier RTW, the care programme is considered cost-effective in comparison with usual care in women undergoing benign gynaecological surgery. Policy makers should investigate how these monetary benefits can be distributed across stakeholders.

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Contributorship statement

All named authors made substantial contributions to this study and the article. EVB, HAB, JRA, and JAH participated in the design and/or execution of the study, the interpretation of data, and the drafting and/or revision of the article. JEB and JMD were involved in the statistical data analyses and interpretation of the data, and the revision of the article. All named authors approved the final version of the manuscript. EVB and JAH are the study guarantors.

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Competing interests statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. Dr. Anema reports a chair in Insurance Medicine paid by the Dutch Social Security Agency, and he is stockholder of Evalua LTD. Dr. Huirne reports grants from Samsung, grants from Gideon Richter, grants from Celonova, outside the submitted work. Dr. Brölmann reports grants from Olympus, personal fees from Nordic Farma, during the conduct of the study . Dr. Anema and dr. Huirne are currently setting up a

spin-off company concerning the implementation of a mobile application concerning the IKHERSTEL intervention in the Netherlands. The remaining authors have nothing to disclose.

Ethics approval

The study protocol was approved by the Institutional Review Board of the VU University Medical Centre (16 May 2011, no. 2011/142) and by the medical ethics committees of all other participating Onze Lieve Vrouwe Gasthuis Oost (Amsterdam), Meander Medical Center (Amersfoort), Amstelland Hospital (Amsterdam), Medical Center Alkmaar (Alkmaar), Diakonessenhuis (Utrecht), Spaarne Gasthuis (locations Haarlem and Hoofddorp), and Flevo Hospital (Almere). Informed consent was obtained from all participants.

Data sharing

No additional data are available, though details on statistical analyses are available from the corresponding author on request.

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Figure 1 Trial profile

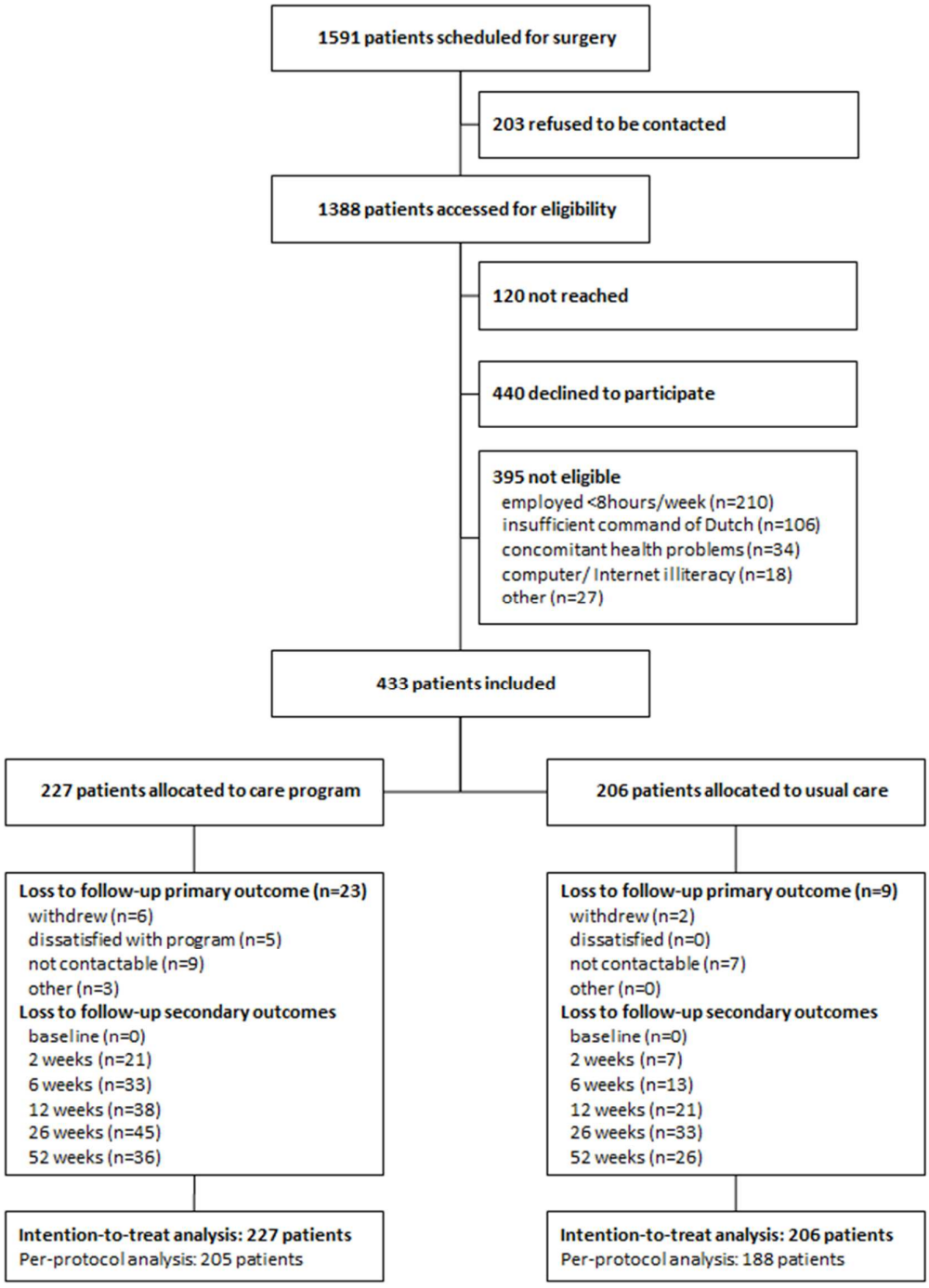
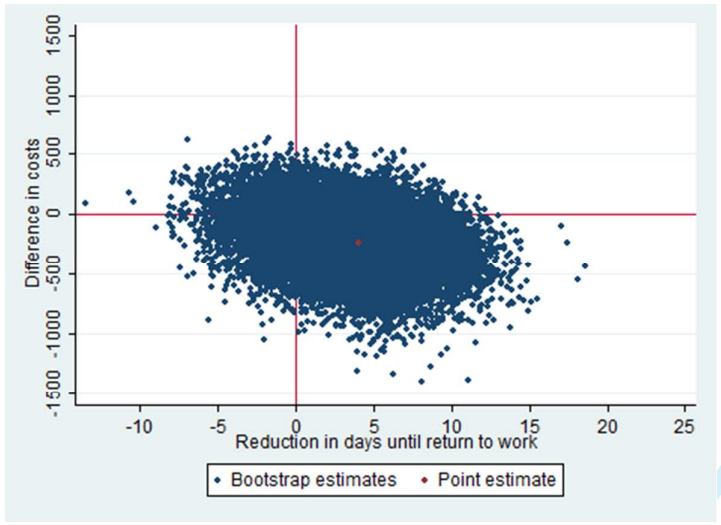
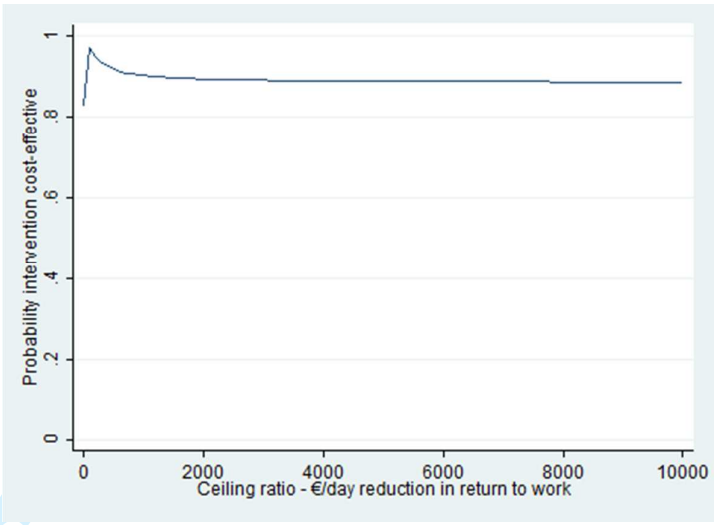


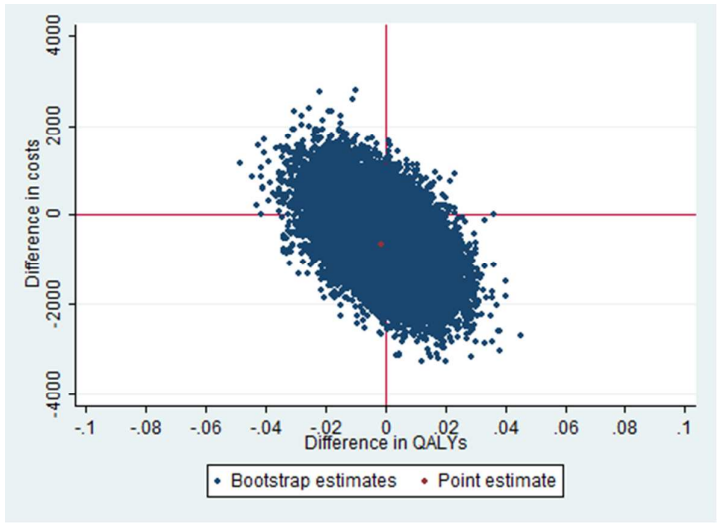
Figure 2 Cost-effectiveness planes and cost-effectiveness acceptability curves for RTW and QALYs



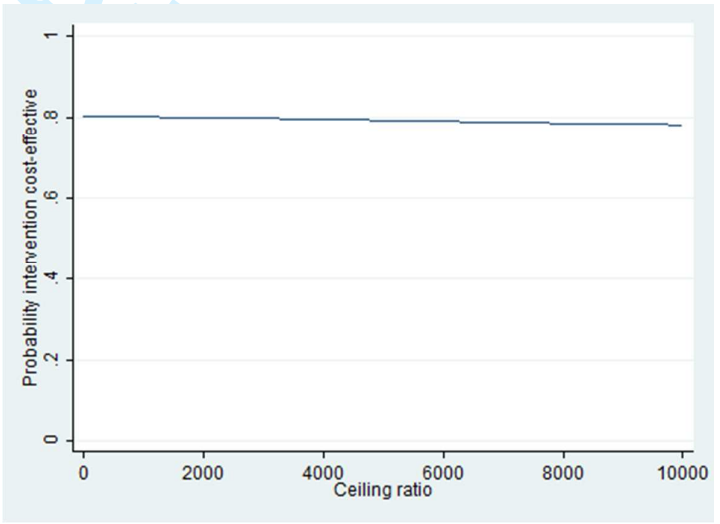
a.



b.



c.



d.

The cost-effectiveness planes (a,c) indicate the uncertainty around the incremental cost-effectiveness ratio.

The cost-effectiveness acceptability curves (b,d) indicate the probability of cost-effectiveness for different values (€) of willingness to pay per unit of effect gained.

RTW, return to work; QALY, Quality Adjusted Life Year.

Table 1 Baseline characteristics of individual patients

	Care Programme (n=227)	Usual Care (n=206)
Patient characteristics		
Age (years ± SD)	46.1 ± 7.3	45.6 ± 6.7
Dutch nationality	220 (96.9%)	202 (98.1%)
Internet use (days/week)		
< 1	2 (0.9%)	3 (1.5%)
1 – 2	9 (4.0%)	10 (4.9%)
3 – 5	45 (19.8%)	42 (20.4%)
> 5	171 (75.3%)	151 (73.3%)
Education level *		
Low	25 (11.0%)	17 (8.3%)
Intermediate	88 (38.8%)	100 (48.5%)
High	114 (50.2%)	89 (43.2%)
Surgery-related characteristics		
Type of surgery		
Adnexal surgery	74 (32.6%)	51 (24.8%)
Laparoscopic hysterectomy	65 (28.6%)	50 (24.3%)
Vaginal hysterectomy	36 (15.9%)	53 (25.7%)
Abdominal hysterectomy	52 (22.9%)	52 (25.2%)
Health-related characteristics		
Perceived health status (mean ± SD)	75.8 ± 16.5	76.9 ± 16.7
Work-related characteristics		
Type of work		
Salary employed	194 (85.5%)	175 (85.0%)
Self-employed	28 (12.3%)	28 (13.6%)
Voluntary work	5 (2.2%)	3 (1.5%)
Work hours per week (mean ± SD)	29.7 ± 9.3	28.7 ± 8.2
Sick leave (3 months before surgery)		
Absence from work §	88 (38.8%)	66 (32.0%)
Number of sick leave days (median (IQR))	4.0 (2-10)	4.5 (2-11)
RTW expectation (long) †	42 (18.5%)	38 (18.4%)
RTW intention (low) ‡	45 (19.8%)	67 (32.5%)

Data are number of patients (%), unless otherwise indicated.
* Low=preschool, primary school; intermediate=secondary school; high=tertiary school, university, or postgraduate.
§ Defined as at least 1 day absence.
† Defined as expectation longer than 3 weeks for adnexal surgery, longer than 6 weeks for laparoscopic or vaginal hysterectomy, or longer than 8 weeks for abdominal hysterectomy.
‡ Defined as score 4 or 5 (range 1-5).
RTW, return to work.

Table 2 Costs associated with self-reported service used across treatment groups at 12 months follow-up

Cost category	Intervention mean (SEM) n=227	Usual care mean (SEM) n=206	Mean cost difference (95% CI)*
Healthcare costs	**3823 (99)**	**4142 (134)**	**-61 (-361 to 218)**
Surgery costs	3236 (64)	3413 (58)	34 (-118 to 174)
Primary care costs	179 (24)	167 (30)	14 (-58 to 95)
Secondary care costs	242 (42)	458 (98)	-178 (-400 to -31)
Costs of medication and aids	13 (4)	10 (4)	3 (-6 to 11)
Home help costs	72 (24)	94 (26)	-19 (-85 to 45)
Intervention	80 (0)	NA	80 (NA)
Lost productivity costs	**8443 (543)**	**9653 (528)**	**-570 (-1909 to 692)**
Costs of absenteeism from unpaid work	1845 (224)	2124 (299)	-144 (-756 to 282)
Costs of absenteeism from paid work	6499 (425)	7281 (344)	-424 (-1469 to 578)
Presenteeism costs	99 (78)	248 (127)	-154 (-458 to 82)
Total societal costs	**12266 (596)**	**13795 (602)**	**-647 (-2116 to 735)**

Costs are expressed in 2014 Euros (€1.00 = £0.85; $1.06).
Mean values summarize the costs derived after the imputation process.
* Uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery
SEM, standard error; CI, confidence interval; NA, not applicable.

Table 3 Effects across treatment groups at 12 months follow-up

Outcomes	Intervention Mean (SEM) n=227	Usual care Mean (SEM) n=206	Mean effect difference (95% CI) *
Duration until RTW (days)	49.6 (2.7)	56.2 (2.2)	-4.1 (-10.8 to 2.6)
QALY's gained	0.96 (0.008)	0.96 (0.007)	-0.001 (-0.023 to 0.020)
HR-QoL (SF-36)			
PCS	5.7[§] (0.7)	6.7[§] (0.6)	-0.7 (-2.6 to 1.1)
MCS	3.3[§] (0.7)	3.7[§] (0.8)	-0.4 (-2.5 to 1.7)
Recovery (RI-10)	24.3[§] (0.4)	25.0[§] (0.5)	-0.6 (-2.0 to 0.9)

* Uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery.
[§] Difference between baseline score and score at 12 months follow-up.
SEM, standard error; CI, confidence interval; RTW, return to work; QALY, Quality Adjusted Life Year; HR-QoL, health-related quality of life; SF, Short Form; PSC, physical component scale; MSC, mental component scale; RI, recovery index.

Table 4 Differences in pooled means costs and effects, incremental cost-effectiveness ratios and the distribution of incremental cost-effectiveness pairs around the quadrants of the cost-effectiveness planes (main analysis)

Outcome	**Δ Cost*** (€) mean (95% CI)	**Δ Effect*** (days) mean (95% CI)	**ICER** €/day	**Distribution CE-plane**			
				NE[1]	**SE**[2]	**SW**[3]	**NW**[4]
RTW	-228 (-708 to 136)	4.1[§] (-2.6 to 10.8)	-56	15%	69%	10%	6%
QALY's gained	-647 (-2116 to 735)	-0.001 (-0.023 to 0.020)	501187	4%	42%	35%	19%
HR-QoL (SF36)							
PCS	-647 (-2116 to 735)	-0.7 (-2.6 to 1.1)	870	6%	19%	58%	17%
MCS	-647 (-2116 to 735)	-0.4 (-2.5 to 1.7)	1573	10%	33%	44%	13%
Recovery (RI-10)	-647 (-2116 to 735)	-0.6 (-2.0 to 0.9)	1127	5%	22%	55%	18%

* uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery

§ Note that a positive value indicates faster RTW in the intervention group compared to the control group.

[1] Refers to the northeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and more costly than usual care.

[2] Refers to the southeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and less costly than usual care.

[3] Refers to the southwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and less costly than usual care.

[4] Refers to the northeast quadrant of the CE-plane, indicating that the intervention care programme is less effective and more costly than usual care.

ICER, Incremental Cost-Effectiveness Ratio; CE plane, cost-effectiveness plane; RTW, return to work; QALY, Quality Adjusted Life Year; HR-QoL, health-related quality of life; SF, Short Form; PSC, physical component scale; MSC, mental component scale; RI, recovery index.

Table 5 Results from the per-protocol and sensitivity analyses (Return to Work)

Analysis	Sample size		Δ Cost* (€)	Δ Effect* (days)	ICER	Distribution CE-plane			
	IC	UC	mean (95% CI)	mean (95% CI)	€/day	NE[1]	SE[2]	SW[3]	NW[4]
Per-protocol analysis	205	188	-359 (-866 to -11)	6.4[§] (-0.2 to 12.9)	-56	8%	87%	5%	1%
Complete-case analysis	154	150	-45 (-466 to 362)	11.6[§] (-5.4 to 19.3)	-4	45%	55%	0%	0%
Friction cost approach	227	206	-228 (-708 to 136)	4.1[§] (-2.6 to 10.8)	-56	15%	69%	10%	6%
Healthcare perspective	227	206	-61 (-361 to 218)	4.1[§] (-2.6 to 10.8)	-15	28%	56%	5%	10%

* uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery

[§] Note that a positive value indicates faster RTW in the intervention group compared to the control group.

[1] Refers to the northeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and more costly than usual care.

[2] Refers to the southeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and less costly than usual care.

[3] Refers to the southwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and less costly than usual care.

[4] Refers to the northwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and more costly than usual care.

IC, intervention care; UC, usual care; ICER, Incremental Cost-Effectiveness Ratio; CE plane, cost-effectiveness plane.

Supplementary table S1 Costs of the intervention care programme from the societal perspective, valued using a bottom-up micro-costing approach

Intervention component	Cost category	Staff	Units	Unit Price	Total costs (n=227)	Costs per patient
Implementation costs						
Training sessions	labour costs	principal investigator	5 hours	€ 36.94	€ 184.69	€ 0.81
(care-managers)	labour costs	occupational physicians	18 hours	€ 89.68	€ 1,614.24	€ 7.11
	labour costs	occupational therapist	2 hours	€ 46.32	€ 92.64	€ 0.41
	capital costs		5 hours	€ 6.26	€ 31.29	€ 0.14
Training sessions	labour costs	principal investigator	38 hours	€ 36.94	€ 1,403.67	€ 6.18
(hospital staff)	travel costs	principal investigator	582 km	€ 0.22	€ 127.28	€ 0.56
	labour costs	gynaecologists	18.9 hours	€ 107.30	€ 2,027.90	€ 8.93
	labour costs	residents	18.9 hours	€ 42.58	€ 804.82	€ 3.55
	labour costs	nurses	45 hours	€ 42.64	€ 1,918.58	€ 8.45
	capital costs		9 hours	€ 6.26	€ 56.33	€ 0.25
	printed materials				€ 821.00	€ 3.62
					Subtotal	**€ 40.01**
eHealth intervention						
Electronic approval	labour costs	gynaecologists	14.2 hours	€ 107.30	€ 1,523.60	€ 6.71
	capital costs		14.2 hours	€ 4.17	€ 59.15	€ 0.26
Maintenance	labour costs	computer specialist	12.2 hours	€ 37.82	€ 461.45	€ 2.03
	capital costs		12.2 hours	€ 1.67	€ 20.33	€ 0.09
Administrator time	labour costs	research assistant	37.8 hours	€ 33.42	€ 1,263.23	€ 5.56
	capital costs		37.8 hours	€ 4.17	€ 157.46	€ 0.69
Website hosting	other		40 months	€ 18.84	€ 578.88	€ 2.55
					Subtotal	**€ 17.90**
Occupational intervention						
Pre-operative consultations	labour costs	occupational physicians	7.9 hours	€ 89.68	€ 708.47	€ 3.12

	capital costs		7.9 hours	€ 4.17	€ 32.91	€ 0.14
	phone costs		413 minutes	€ 0.09	€ 38.71	€ 0.17
Post-operative consultations	labour costs	occupational physicians	37.5 hours	€ 89.68	€ 3.363.00	€ 14.81
	capital costs		37.5 hours	€ 4.17	€ 156.21	€ 0.69
	phone costs		2083 minutes	€ 0.09	€ 195.23	€ 0.86
Workplace intervention	labour costs	occupational therapist	4 hours	€ 46.32	€ 185.29	€ 0.82
	capital costs		3 hours	€ 6.26	€ 18.78	€ 0.08
	labour costs	employer	2 hours	€ 83.69	€ 167.37	€ 0.74
	travel costs	occupational therapist	110 km	€ 0.22	€ 24.06	€ 0.11
					Subtotal	**€ 21.54**
Developmental costs					€ 33,873.55	€ 0.56 [§]
					Subtotal	**€ 0.56**
TOTAL intervention costs						**€ 80.02**

Costs are expressed in 2014 Euros (€1.00 = £0.85; $1.06).

[§] € 33,873.55 was paid for the development of the intervention care-programme. For calculating the development costs per participant, these were divided by the expected number of users during the first five years after implementation (60,200). Per year 20,000 gynaecologic surgeries (LAS, TLH, VH, AH) are being performed in the Netherlands and based on the outcomes of an earlier performed process-evaluation we hypothesized a reach of 60.2%.[42]

Supplementary table S2 Differences in pooled means costs and effects, incremental cost-effectiveness ratios and the distribution of incremental cost-effectiveness pairs around the quadrants of the cost-effectiveness plane

Analysis	Sample size IC	UC	Δ Cost* (€) mean (95% CI)	Δ Effect* (days) mean (95% CI)	ICER €/day	Distribution CE-plane NE[1]	SE[2]	SW[3]	NW[4]
QALYs									
Intention to treat	227	206	-647 (-2116 to 735)	-0.001 (-0.023 to 0.020)	501187	4%	42%	35%	19%
Per-protocol analysis	205	188	-1148 (-2611 to 162)	0.003 (-0.019 to 0.024)	-432881	1%	59%	34%	6%
Complete-case analysis	132	136	-1607 (-3421 to 52)	0.009 (-0.013 to 0.033)	-202816	1%	72%	24%	3%
Friction cost approach	227	206	-825 (-2209 to 470)	-0.001 (-0.023 to 0.020	639131	2%	44%	42%	12%
Healthcare perspective	227	206	-61 (-361 to 218)	-0.001 (-0.023 to 0.020	46942	13%	33%	28%	26%
SF-36 PHYSICAL COMPONENT SCORE									
Intention to treat	227	206	-647 (-2116 to 735)	-0.7 (-2.6 to 1.1)	870	6%	19%	58%	17%
Per-protocol analysis	205	188	-1148 (-2611 to 162)	-0.9 (-2.8 to 1.1)	1350	2%	21%	71%	6%
Complete-case analysis	153	149	-1689 (-3316 to -231)	-1.2 (-3.3 to 0.8)	1389	0%	12%	86%	2%
Friction cost approach	227	206	-825 (-2209 to 470)	-0.7 (-2.6 to 1.1)	1109	4%	21%	64%	11%
Healthcare perspective	227	206	-61 (-361 to 218)	-0.7 (-2.6 to 1.1)	81	8%	17%	44%	31%
SF-36 MENTAL COMPONENT SCALE									
Intention to treat	227	206	-647 (-2116 to 735)	-0.4 (-2.5 to 1.7)	1573	10%	33%	44%	13%
Per-protocol analysis	205	188	-1148 (-2611 to 162)	-0.5 (-2.7 to 1.7)	2198	2%	32%	61%	5%
Complete-case analysis	153	149	-1689 (-3316 to -231)	-0.1 (-2.6 to 1.9)	12598	1%	49%	49%	1%
Friction cost approach	227	206	-825 (-2209 to 470)	-0.4 (-2.5 to 1.7)	2006	6%	37%	49%	8%
Healthcare perspective	227	206	-61 (-361 to 218)	-0.4 (-2.5 to 1.7)	147	17%	26%	35%	22%
RECOVERY INDEX									
Intention to treat	227	206	-647 (-2116 to 735)	-0.6 (-2.0 to 0.9)	1127	5%	22%	55%	18%
Per-protocol analysis	205	188	-1148 (-2611 to 162)	-0.7 (-2.1 to 0.8)	1786	1%	23%	70%	6%
Complete-case analysis	153	149	-1689 (-3316 to -231)	-0.7 (-2.2 to 0.7)	2562	1%	20%	78%	1%
Friction cost approach	227	206	-825 (-2209 to 470)	-0.6 (-2.0 to 0.9)	1437	3%	24%	62%	12%
Healthcare perspective	227	206	-61 (-361 to 218)	-0.6 (-2.0 to 0.9)	106	8%	19%	42%	31%

* uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery
[1] Refers to the northeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and more costly than usual care.
[2] Refers to the southeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and less costly than usual care.
[3] Refers to the southwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and less costly than usual care.
[4] Refers to the northwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and more costly than usual care.
IC, intervention care; UC, usual care; ICER, Incremental Cost-effectiveness Ratio; CE plane, cost-effectiveness plane.

CHEERS checklist

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.	page 1, line 6.
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.	page 2, line 3 to 28.
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.	page 3, line 4 to 14; page 3, line 14 to 22.
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page 5, line 4 to 9; page 9, line 9 to 17.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page 4, line 33 to page 5, line 2.
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page 4, line 26 to 28.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	page 5, line 21 to page 6, line 9; page 6, line 11 to 18.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page 4, line 29 to 30; page 8, line 12 to 13.
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	page 8, line 12 to 13.
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.	page 6 , line 21 to 33.
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	page 4, line 25 to 28; page 5, line 22 to page 6, line 9.

Section/item	Item No	Recommendation	Reported on page No/line No
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	n/a
Estimating costs and resources	13a	*Single study-based economic evaluation*: 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.	page 7, line 1 to 24.
Currency, price date and conversion	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.	page 8, line 12 to 13; table 2.
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.	Page 8, line 25 to 32.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	page 8, line 18 to 23.
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.	page 8, line 18 to 23; page 9, line 1 to 7.
Results			
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.	page 10, line 1 to 19; table 2 and 3; table S1
Incremental costs and outcomes	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.	page 10, line 22 to page 11, line 12; table 4;
Characterising uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	page 11, line 14 to 23.

Section/item	Item No	Recommendation	Reported on page No/line No
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.	page 11, line 25 to page 12, line 12; page 13, line 19 to 27.
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.	page 12, line 14 to page 14, line 21; page 15, line 20 to 30.
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.	page 16, line 20 to 25.
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.	page 16, line 27 to page 17, line 2.

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Cost-effectiveness of an Internet-based perioperative care programme to enhance postoperative recovery in gynaecological patients: economic evaluation alongside a stepped-wedge cluster-randomised trial

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Title Page

Full title:

Cost-effectiveness of an Internet-based perioperative care programme to enhance postoperative recovery in gynaecological patients: economic evaluation alongside a stepped-wedge cluster-randomised trial

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Abstract

Objectives To evaluate the cost-effectiveness and cost-utility of an Internet-based perioperative care programme compared with usual care for gynaecological patients.

Design Economic evaluation from a societal perspective alongside a stepped-wedge cluster-randomised controlled trial with 12 months follow-up.

Setting Secondary care, nine hospitals in the Netherlands, 2011-2014.

Participants 433 employed women aged 18-65 scheduled for a hysterectomy and/or laparoscopic adnexal surgery.

Intervention The intervention comprised an Internet-based care programme aimed at improving convalescence and preventing delayed return to work following gynaecological surgery was sequentially rolled out. Depending on the implementation phase of their hospital, patients were allocated to usual care (n=206) or to the intervention (n=227).

Main outcome measures The primary outcome was duration until full sustainable return to work (RTW). Secondary outcomes were quality adjusted life years (QALYs), health-related quality of life and recovery.

Results At 12 months, there were no statistically significant differences in total societal costs (€-647; 95% CI €-2116 to €753) and duration until RTW (-4.1; 95% CI -10.8 to 2.6) between groups. The incremental cost-effectiveness ratio (ICER) for RTW was 56; each day earlier RTW in the intervention group was associated with cost savings of 56 euros compared to usual care. The probability of the intervention being cost-effective was 0.79 at a willingness-to-pay (WTP) of €0 per day earlier RTW, which increased to 0.97 at a WTP of €76 per day earlier RTW. The difference in QALYs gained over 12 months between the groups was clinically irrelevant resulting in a low probability of cost-effectiveness for QALYs.

Conclusions Considering that on average the costs of a day of sickness absence are €230, the care programme is considered cost-effective in comparison with usual care for duration until sustainable RTW after gynaecological surgery for benign disease. Future research should indicate whether widespread implementation of this care programme has the potential to reduce societal costs associated with gynaecological surgery.

Trial registration Netherlands National Trial Register NTR2933.

Key words gynaecology; Internet; telemedicine; self-management; convalescence; return to work; economic evaluation.

Strengths and limitations of this study

- This is the first economic evaluation on an Internet-based care programme aimed at improving convalescence and preventing delayed return to work following gynaecological surgery.
- The study was conducted alongside a cluster-randomised controlled trial allowing prospective collection of relevant cost and effect data.
- The study was performed from a societal perspective and costs associated with lost productivity included both absenteeism as well as presenteeism costs.
- A latent barrier to future acceptance and implementation of the care programme lies in the fact that the costs and benefits of the care programme are separated between different types of stakeholders.

Main document

Introduction

At present, there is a transition of perioperative care from the hospital setting towards the home environment.[1-4] The introduction of advanced surgical techniques in combination with the implementation of "fast-track" clinical pathways have considerably reduced the length of postoperative hospital stays and many (complex) surgeries are now being performed in an ambulatory setting.[5-7] This is beneficial from the perspective of the healthcare system, as it leads to the containment of healthcare costs.[1, 8]

However, costs associated with lost productivity following surgery contribute to the total societal costs of surgical procedures as well, and are mostly not taken into account. Moreover, there is considerable evidence that the duration of sick leave following gynaecological surgery generally exceeds the period considered appropriate by specialists.[9] Therefore, preventing unnecessary prolonged recovery following gynaecological surgery, may translate into considerable savings for society.

We developed an Internet-based care programme for patients undergoing gynaecological surgery for benign disease, aimed at facilitating recovery after discharge and preventing delayed return to work.[10, 11] In this paper, we report on the cost-effectiveness and cost-utility of the Internet-based care programme compared to usual care. The findings on clinical effectiveness were reported in a separate paper.

Methods

Study design and participants

This economic evaluation was performed from a societal perspective and was carried out alongside a stepped-wedge cluster randomised controlled trial comparing an Internet-based care programme with usual care for patients undergoing benign gynaecological surgery. The study was done in the Netherlands between October 2011 and July 2014. The follow-up period was 12 months. The trial protocol has been published previously in accordance to CONSORT extended guidelines.[9]

The clusters in this trial were formed by separate hospitals. A total of nine hospitals participated, which were selected before the start of the trial. Hospitals were eligible if they

performed at least 100 hysterectomies or laparoscopic adnexal surgeries annually, and were located within 50km of the VU medical centre, Amsterdam, the Netherlands.

Patients were recruited from the waiting lists for hysterectomy (abdominal, vaginal or laparoscopic) and laparoscopic adnexal surgery. Eligible participants were women aged 18-65 who were employed for at least eight hours a week (unpaid or paid employment, or self-employed). We excluded patients who had severe benign comorbidity, had a malignancy, were pregnant, were computer or Internet illiterate, were involved in a lawsuit against their employer, were on disability sick leave before surgery, or had insufficient command of Dutch.

Randomisation and blinding

Randomization took place at the level of the clusters and determined the order in which the intervention was implemented in the participating hospitals. The sequence was generated by a statistician using a computer generated list of random numbers. A stepped wedge approach was employed as it enabled us to study the implementation process as well.[9]

Patients, clinicians and researchers could not be blinded for the intervention. However, group allocation was concealed until patients had agreed to participate and provided written informed consent. Data analysts (EB, JB) were masked to group allocation.

Intervention care programme and implementation strategy

The development and content of the intervention care programme have been described elsewhere in more detail.[9, 11] A multi-faceted implementation strategy was employed to achieve maximal adoption of the care programme, targeting three different levels.

At the level of the organization, the structure of healthcare was changed by the introduction of the interactive web portal that was accessible for patients as well as their healthcare professionals. In addition, care managers were trained to help patients identify possible barriers to resuming work activities and could assist, if necessary, in the planning and execution of work resumption, before and after surgery.

At the level of the healthcare professional, educational training sessions were organised to introduce an earlier developed guideline on postoperative convalescence recommendations to stimulate evidence-based patient education.[10]

At the patient level, the care programme consisted of two steps. First, all participants allocated to the intervention group received access to the web portal several weeks prior to their surgery (eHealth intervention). The interactive web portal facilitated self-management by providing patients with individual tailored convalescence recommendations throughout the entire surgical pathway as well as monitoring recovery postoperatively through an interactive self-assessment tool. Second, for those patients at risk of prolonged sick leave, a care manager was available to provide additional guidance in the process of resuming work activities (occupational intervention).

Usual Care

Before the care programme was implemented in the hospitals, participating patients received usual care. Although considerable variation in usual care exists in the Netherlands, postoperative patients generally receive verbal instructions at discharge by a nurse and/or physician, sometimes accompanied by a letter or brochure. Usually, a postoperative consultation is planned six weeks after surgery. Due to Dutch legislation, employed patients who do not resume work within 6 weeks after the surgery are invited for a consultation with their occupational physician.

Main outcome measures

The primary outcome was duration until sustainable return to work (RTW) defined as the resumption of own work or other work with equal earnings, for at least 4 weeks without (partial or full) recurrence of sick leave.[12] Data on return to work were collected by means of monthly electronic sick leave calendars.

Quality adjusted life years (QALYs) was one of the secondary outcomes and was measured using the Dutch version of the EuroQol five-dimensional questionnaire (EQ-5D-3L).[13] The Dutch tariff was used to estimate the utility of EQ-5D-3L health states.[14] QALYs were calculated by multiplying the utility with the amount of time a patient spent in a particular health state. Transitions between health states were linearly interpolated. Other secondary outcomes included health-related quality of life assessed by Short-Form Health Survey (SF-36)[15], and recovery assessed by the Recovery Index (RI-10).[16] All secondary outcomes were assessed at baseline, and at 2, 6, 12, 26, and 52 weeks follow-up.

Service use and costs

The intervention and implementation strategy costs consisted of costs related to implementing the new care programme. A bottom-up micro-costing approach was used for estimating intervention costs, using detailed data regarding the quantity and unit prices of: (1) the training sessions of involved healthcare professionals (clinical staff, occupational physicians, occupational therapist), (2) the eHealth intervention (hosting of web portal, administrator time), and (3) the occupational intervention (number and duration of consultations).[17]

Data on healthcare services used and support received by the participants were collected using electronic questionnaires during one year. Each month, the patient was asked to report service use over the previous month. Patients who were not sick listed and did not have any healthcare costs during three consecutive months, received a shortened version of the questionnaire. In case of no response, electronic reminders were sent after one and two weeks. If participants did not respond to the electronic reminders either, an additional attempt was made to complete the missing data per email, mail or telephone every three months.

Only healthcare utilization and support related to the gynaecological surgery were collected, and included the following categories: surgery and initial hospitalization, primary and secondary care including complementary medicine, medication and medical aids, home care and informal help.

Service utilization was valued using Dutch standard costs.[18] If these were unavailable, prices according to professional organizations were used. The prices of prescribed drugs were estimated using the prices of the Royal Dutch Society for Pharmacy.[19]

Productivity Loss

Absenteeism costs were calculated using the Human Capital Approach (HCA). The net number of sick leave days during follow-up were multiplied by the estimated costs of one day of sick leave for females, stratified for age.[18] In case of partial sick leave, we assumed that participants were 100% productive during the hours of partial work resumption.

Presenteeism (i.e. reduced productivity while at work) was assessed monthly after full resumption of work using two items of the "Productivity and Disease Questionnaire" (PRODISQ).[20] Patients were asked to report the quantity (q1) and quality (q2) of the work

performed during the latest day at work on an 11-point scale, ranging from "nothing/very bad quality" (0) to "same as normal"(10).

The level of presenteeism ($Pres_{day}$) on the latest day at work was calculated using the following formula: $Pres_{day} = (1-((q1*q2)/100))$.[20,21] Assuming linearity, the level of presenteeism on the latest day at work was then extrapolated over the total month. The total number of workdays lost due to presenteeism were calculated ($Pres_{month}$) by multiplying the participants' presenteeism level by their number of days worked during that month. Subsequently, presenteeism costs per month were calculated by multiplying $Pres_{month}$, by the estimated costs of one day of lost productivity.

The index year of the study was 2014. Discounting of costs was not necessary because the follow-up was one year.[22]

Statistical analysis

The sample size of the study (n=454) was calculated for detecting a relevant difference in return to work (hazard ratio (HR) of 1.5) in the main outcome study.[9] The economic evaluation was done according to the intention to treat principle. Missing cost and effect data during follow-up were imputed using multiple imputation by chained equations (MICE). Multiple imputation was done using SPSS 16.0 with predictive mean matching. An imputation model containing demographic and prognostic variables was used to create five complete datasets after which the loss of efficiency was smaller than 5%.[23] Rubin's rules were used to pool effects and costs from the five imputed datasets.[24]

Differences in costs and effects were estimated using linear multilevel regression analyses, while adjusting for type of surgery. Clustering at the hospital- and patient-level was accounted for in these multilevel models. For the cost-effectiveness and cost-utility analyses, we calculated incremental cost-effectiveness ratios (ICERs) by dividing the incremental costs by the incremental effects. The ICER indicates the additional investments needed for the intervention to gain one extra unit of effect compared with usual care. In the ICER for duration until RTW, productivity costs due to sick leave were excluded from the cost estimates to avoid double counting.

We used non-parametric bootstrapping with 5000 replications to estimate 95% confidence intervals around cost differences and the uncertainty surrounding the ICERs.[25] To account for the clustering of data, bootstrap replications were stratified for hospital.[26] Bootstrapped cost-effect pairs were plotted on cost-effectiveness planes (CE planes) and used to estimate cost-effectiveness acceptability curves (CEA curves). CEA curves show the probability that a treatment is cost effective in comparison with the control treatment at a specific ceiling ratio, which is the amount of money society is willing to pay to gain one extra unit of effect.

Sensitivity analyses

To assess whether protocol deviations influenced the treatment effect, a per-protocol analysis was performed. In addition, to assess the robustness of the results, we carried out three sensitivity analyses. Firstly, we did a complete-case analysis to assess the cost-effectiveness of the interventions excluding patients who were lost to follow-up. Secondly, we replicated the cost-effectiveness analysis using the Friction Cost Approach. The FCA assumes that costs are limited to the friction period (i.e. the period needed to replace a sick worker). A friction period of 23 weeks and an elasticity of 0.8 was used. Thirdly, an analysis from the healthcare perspective was performed including only healthcare costs.

All statistical analyses followed a predefined analysis plan and were done in SPSS (version 16.0) and STATA (version 12SE).

Results

Participants

During the study period, 1591 patients were scheduled for a hysterectomy and/or laparoscopic adnexal surgery in the participating hospitals. In total, 433 patients enrolled in the study, 206 patients during the control phase and 227 patients during intervention phase (figure 1).

Participants' demographic and prognostic variables are presented in table 1. Complete follow-up data were obtained from 92.6% of the participants on the primary outcome RTW, from 71.8% on the secondary outcomes, and 70.0% on healthcare utilization. Baseline characteristics did not differ between participants with and without complete cost data, except that patients with complete data on healthcare utilization used the Internet more frequently than women with incomplete data.

Table 1 Baseline characteristics of individual patients

	Care Programme (n=227)	Usual Care (n=206)
Patient characteristics		
Age (years ± SD)	46.1 ± 7.3	45.6 ± 6.7
Dutch nationality	220 (96.9%)	202 (98.1%)
Internet use (days/week)		
< 1	2 (0.9%)	3 (1.5%)
1 – 2	9 (4.0%)	10 (4.9%)
3 – 5	45 (19.8%)	42 (20.4%)
> 5	171 (75.3%)	151 (73.3%)
Education level *		
Low	25 (11.0%)	17 (8.3%)
Intermediate	88 (38.8%)	100 (48.5%)
High	114 (50.2%)	89 (43.2%)
Surgery-related characteristics		
Type of surgery		
Adnexal surgery	74 (32.6%)	51 (24.8%)
Laparoscopic hysterectomy	65 (28.6%)	50 (24.3%)
Vaginal hysterectomy	36 (15.9%)	53 (25.7%)
Abdominal hysterectomy	52 (22.9%)	52 (25.2%)
Health-related characteristics		
Perceived health status (mean ± SD)	75.8 ± 16.5	76.9 ± 16.7
Work-related characteristics		
Type of work		
Salary employed	194 (85.5%)	175 (85.0%)
Self-employed	28 (12.3%)	28 (13.6%)
Voluntary work	5 (2.2%)	3 (1.5%)
Work hours per week (mean ± SD)	29.7 ± 9.3	28.7 ± 8.2
Sick leave (3 months before surgery)		
Absence from work §	88 (38.8%)	66 (32.0%)
Number of sick leave days (median (IQR))	4.0 (2-10)	4.5 (2-11)
RTW expectation (long) †	42 (18.5%)	38 (18.4%)
RTW intention (low) ‡	45 (19.8%)	67 (32.5%)

Data are number of patients (%), unless otherwise indicated.
* Low=preschool, primary school; intermediate=secondary school; high=tertiary school, university, or postgraduate.
§ Defined as at least 1 day absence.
† Defined as expectation longer than 3 weeks for adnexal surgery, longer than 6 weeks for laparoscopic or vaginal hysterectomy, or longer than 8 weeks for abdominal hysterectomy.
‡ Defined as score 4 or 5 (range 1-5).
RTW, return to work.

Service use and costs

Table 2 presents the costs of self-reported service use per category over the 12 months of follow-up stratified by treatment group and the mean cost differences between both groups.

Intervention costs were €80 per participant (online supplementary table S1). Total societal costs per patient were €12,266 in the intervention group and €13,795 in the usual care group. After correction for clustering by hospital and adjustment for surgery type, total societal costs in the intervention group were €647 lower compared to the usual care group, but this difference was not statistically significant (95% CI €-2116 to €753). In both groups, costs related to productivity losses were about two times higher than total healthcare costs. There was no statistical significant differences in healthcare costs between the intervention group and usual care group (€-61; 95% CI €-361 to €218) and lost productivity costs (€-570; 95% CI €-1909 to €692). Only costs for secondary care were significantly lower in the intervention group compared to the usual care group (€-178; 95% CI €-400 to €-31).

Table 2 Costs associated with self-reported service used across treatment groups at 12 months follow-up

Cost category	Intervention mean (SEM) n=227	Usual care mean (SEM) n=206	Mean cost difference (95% CI)*
Healthcare costs	**3823 (99)**	**4142 (134)**	**-61 (-361 to 218)**
Surgery costs	3236 (64)	3413 (58)	34 (-118 to 174)
Primary care costs	179 (24)	167 (30)	14 (-58 to 95)
Secondary care costs	242 (42)	458 (98)	-178 (-400 to -31)
Costs of medication and aids	13 (4)	10 (4)	3 (-6 to 11)
Home help costs	72 (24)	94 (26)	-19 (-85 to 45)
Intervention	80 (0)	NA	80 (NA)
Lost productivity costs	**8443 (543)**	**9653 (528)**	**-570 (-1909 to 692)**
Costs of absenteeism from unpaid work	1845 (224)	2124 (299)	-144 (-756 to 282)
Costs of absenteeism from paid work	6499 (425)	7281 (344)	-424 (-1469 to 578)
Presenteeism costs	99 (78)	248 (127)	-154 (-458 to 82)
Total societal costs	**12266 (596)**	**13795 (602)**	**-647 (-2116 to 735)**

Costs are expressed in 2014 Euros (€1.00 = £0.85; $1.06).
Mean values summarize the costs derived after the imputation process.
* Uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery
SEM, standard error; CI, confidence interval; NA, not applicable.

Effectiveness

The mean duration until RTW in the intervention group was 49.6 days versus 56.2 days in the usual care group. The adjusted difference in duration until RTW between intervention and usual care was -4.1 days, but this difference was not statistically significant (95% CI -10.8 to 2.6) (table 3). For the other outcomes, no statistically differences were found between both groups at 12 months either.

Table 3 Effects across treatment groups at 12 months follow-up

Outcomes	Intervention Mean (SEM) n=227	Usual care Mean (SEM) n=206	Mean effect difference (95% CI) *
Duration until RTW (days)	49.6 (2.7)	56.2 (2.2)	-4.1 (-10.8 to 2.6)
QALY's gained	0.96 (0.008)	0.96 (0.007)	-0.001 (-0.023 to 0.020)
HR-QoL (SF-36)			
PCS	5.7§ (0.7)	6.7§ (0.6)	-0.7 (-2.6 to 1.1)
MCS	3.3§ (0.7)	3.7§ (0.8)	-0.4 (-2.5 to 1.7)
Recovery (RI-10)	24.3§ (0.4)	25.0§ (0.5)	-0.6 (-2.0 to 0.9)

* Uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery.
§ Difference between baseline score and score at 12 months follow-up.
SEM, standard error; CI, confidence interval; RTW, return to work; QALY, Quality Adjusted Life Year; HR-QoL, health-related quality of life; SF, Short Form; PSC, physical component scale; MSC, mental component scale; RI, recovery index.

Cost-effectiveness

The results of the cost-effectiveness analysis for duration until RTW are presented in table 4. The incremental cost-effectiveness ratio (ICER) for sustainable RTW was 56 indicating that each day earlier RTW in the intervention group is associated with cost savings of 56 euros in comparison with the usual care group. In the cost-effectiveness plane, 69% of the incremental cost effect pairs were located in the south east quadrant indicating that the intervention is more effective and less costly than usual care (figure 2a). The cost-effectiveness acceptability curve presented in figure 2b shows that if the societal willingness-to-pay (WTP) for one earlier day of RTW is €0, the probability that the intervention is cost-effective in comparison with usual care is 0.79. This probability increases to 0.97 at max if the WTP is €76 per day earlier RTW.

As the differences observed for the outcomes health-related quality of life and recovery after 12 months were small and not significant, the ICERs for these outcomes were quite large. In the cost-effectiveness planes, the majority of cost-effect pairs were located in the southern quadrants, indicating the intervention was less expensive. However, the cost-effect pairs were roughly divided between the eastern and western quadrant indicating that the intervention can lead to both better and worse outcomes compared to usual care.

Table 4 Differences in pooled means costs and effects, incremental cost-effectiveness ratios and the distribution of incremental cost-effectiveness pairs around the quadrants of the cost-effectiveness planes (main analysis)

Outcome	**Δ Cost*** (€) mean (95% CI)	**Δ Effect*** (days) mean (95% CI)	**ICER** €/day	**Distribution CE-plane**			
				NE[1]	**SE[2]**	**SW[3]**	**NW[4]**
RTW	-228 (-708 to 136)	4.1[§] (-2.6 to 10.8)	-56	15%	69%	10%	6%
QALY's gained	-647 (-2116 to 735)	-0.001 (-0.023 to 0.020)	501187	4%	42%	35%	19%
HR-QoL (SF36)							
PCS	-647 (-2116 to 735)	-0.7 (-2.6 to 1.1)	870	6%	19%	58%	17%
MCS	-647 (-2116 to 735)	-0.4 (-2.5 to 1.7)	1573	10%	33%	44%	13%
Recovery (RI-10)	-647 (-2116 to 735)	-0.6 (-2.0 to 0.9)	1127	5%	22%	55%	18%

* uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery

[§] Note that a positive value indicates faster RTW in the intervention group compared to the control group.

[1] Refers to the northeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and more costly than usual care.

[2] Refers to the southeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and less costly than usual care.

[3] Refers to the southwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and less costly than usual care.

[4] Refers to the northeast quadrant of the CE-plane, indicating that the intervention care programme is less effective and more costly than usual care.

ICER, Incremental Cost-Effectiveness Ratio; CE plane, cost-effectiveness plane; RTW, return to work; QALY, Quality Adjusted Life Year; HR-QoL, health-related quality of life; SF, Short Form; PSC, physical component scale; MSC, mental component scale; RI, recovery index.

Table 5 Results from the per-protocol and sensitivity analyses (Return to Work)

Analysis	**Sample size**		**Δ Cost*** (€)	**Δ Effect*** (days)	**ICER**	**Distribution CE-plane**			
	IC	**UC**	mean (95% CI)	mean (95% CI)	€/day	**NE[1]**	**SE[2]**	**SW[3]**	**NW[4]**
Per-protocol analysis	205	188	-359 (-866 to -11)	6.4[§] (-0.2 to 12.9)	-56	8%	87%	5%	1%
Complete-case analysis	154	150	-45 (-466 to 362)	11.6[§] (-5.4 to 19.3)	-4	45%	55%	0%	0%
Friction cost approach	227	206	-228 (-708 to 136)	4.1[§] (-2.6 to 10.8)	-56	15%	69%	10%	6%
Healthcare perspective	227	206	-61 (-361 to 218)	4.1[§] (-2.6 to 10.8)	-15	28%	56%	5%	10%

* uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery

[§] Note that a positive value indicates faster RTW in the intervention group compared to the control group.

[1] Refers to the northeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and more costly than usual care.

[2] Refers to the southeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and less costly than usual care.

[3] Refers to the southwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and less costly than usual care.

[4] Refers to the northwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and more costly than usual care.

IC, intervention care; UC, usual care; ICER, Incremental Cost-Effectiveness Ratio; CE plane, cost-effectiveness plane.

Cost-utility

The difference in QALYs gained over 12 months between the two study groups was small and not statistically significant or clinically relevant (table 4). Therefore, the ICER for QALYs became extraordinary large (half million Euros). As a result, the probability that the intervention was cost-effective in comparison with usual care was considerably lower than for the primary outcome (0.77 at WTP is €0 per QALY gained and decreasing at higher WTP values).

Per-protocol analysis

In the per-protocol analysis 40 patients were excluded because they did not receive the care according to protocol due to several reasons: did not fit the inclusion criteria (n=3); had a more severe surgery than planned (n=25), or had a complicated postoperative course and needed a repeat surgery during follow-up (n=12). By excluding those patients, the difference in effect became larger, but was still not significant (-6.4 days, 95% CI -12.9 to 0.20) and the cost differences became statistically significant in favour of the intervention (mean difference €-359, 95% CI -866 to -11) (table 5). Hence, compared to the main analysis, the probability of cost-effectiveness increased considerably at a WTP of €0 per one day earlier RTW (from 0.79 to 0.92).

Sensitivity analyses

The results of the primary outcome in the sensitivity analyses differed in some aspects from the main analysis (table 5). First, in the complete-case analysis, the effect difference between study groups became larger in favour of the intervention group, but the cost savings in the intervention group as compared to usual care became smaller. The probability of cost-effectiveness compared to the main analysis therefore decreased (from 0.79 to 0.55). Second, in the analyses performed from the healthcare perspective, cost savings became much smaller, as costs associated with lost productivity were not taken into account. As a result the probability of cost-effectiveness reduced (from 0.79 to 0.61). Finally, the results from the friction cost analysis were identical to the intention to treat analysis, indicating that the majority of patients returned to their work before the end of the friction period of 23 weeks.

The results of the per-protocol analyses and sensitivity analyses for the secondary outcomes QALYs, health-related quality of life and recovery are presented in online supplementary table S2. In the per-protocol analyses, cost differences became larger in favour of the

intervention group, however, they did not reach statistical significance. The probability of cost-effectiveness at a WTP of €0 per unit of effect increased from 0.77 to 0.93. In contrast to the complete-case analysis for the primary outcome, the complete-case analyses for the secondary outcomes showed a statistical significant increase in cost savings in the intervention group. The probability of cost-effectiveness at a WTP of €0 per unit of effect increased from 0.77 to 0.98

Discussion

In this study, we evaluated the cost-effectiveness and cost-utility of a rigorously designed Internet-based perioperative care programme compared with usual care for gynaecological patients. Our results show that for the primary outcome duration until full resumption of work, the probability that the care programme is cost-effective as compared to usual care is 0.97 at a willingness to pay of €76 per day earlier RTW. Taking into account that the average costs per sick leave day are €230, we conclude that the intervention is cost-effective as compared to usual care.

Interpretation of the findings

In the current economic evaluation, the adjusted mean difference until RTW between study groups was not statistically significant (-4.1 days, 95% CI -10.8 to 2.6). In the accompanying paper on the clinical effectiveness of the intervention, median days until RTW were compared between study arms using Cox regression analyses. However, survival analysis results in difficulties in interpreting the ICER. Therefore, we chose to compare mean days until RTW in the current cost-effectiveness study and used bootstrapping to account for the skewed distribution of this variable.

In addition, the cost-difference between the intervention group and the control group was not statistically significant either, although total societal costs were lower in the intervention group than in the control group. A possible explanation might be that the sample size of this study was based on the primary outcome full sustainable return to work, and, therefore, underpowered to detect relevant cost differences, as cost data are right skewed and require relative large samples.[27]

Secondary care costs in the intervention group were lower compared to the usual care group. Future research should investigate if the care programme truly leads to different health

seeking behaviour. Possibly, patients receiving additional perioperative care were more confident in their own self-management skills preventing them from visiting a healthcare professional. In addition, costs associated with primary care were similar in both groups, demonstrating that the care programme did not cause a shift from secondary care to primary care in the intervention group compared to the usual care group. Concerns of increased workload in the primary care setting due to changes in perioperative care have been reported before, however, seem to be ungrounded.[28, 29]

We did not find any clinical relevant differences in the secondary outcomes. Thus, despite the possible difference in the RTW rates between study groups, this did not have an effect on patients' perceptions about their quality of life and recovery. Possibly, the surgery itself has a much larger impact on these outcomes than the method of postoperative guidance.

The results of the per-protocol analyses, were slightly more favourable than those of the main analyses. Thus, by presenting the intervention to the ideal target population, the probability of cost-effectiveness of the intervention in comparison with usual care increases. This is in concordance with our initial objective to develop Internet-based care programme for women undergoing an uncomplicated surgical procedure.[10] It may be challenging to identify future patients who will benefit most from the care programme, as complications cannot always be predicted pre-operatively. In addition, it should be investigated further what the needs are of patients with a complicated course and how they should best be guided and monitored during their recovery.

Strengths and weaknesses of the study

Several strengths of the present study are noteworthy. First of all, we are not aware of other current perioperative interventions that aim at preventing unnecessary prolonged recovery and reducing sick leave in order to contain societal costs associated with gynaecological surgical care. Second, analyses were performed alongside a pragmatic trial, allowing prospective collection of relevant cost and effect data and enabling the evaluation of the intervention's cost-effectiveness under real world conditions.[27] The third strength concerns the use of linear multilevel analyses to account for possible clustering of data as a result of the chosen study design. Randomization at cluster level was chosen to prevent contamination between the study arms. Moreover, the employment of a stepped wedge design allowed the sequential

implementation of the care programme in the participating hospitals, providing the possibility to study the implementation process as well.

Our study also has limitations. The first limitation is the collection of cost data through self-reported retrospective questionnaires. However, since administrative data on service use are very hard to obtain in the Netherlands, societal cost data can only be collected by means of self-report. In order to prevent recall-bias, we minimised the recall period to only one month. In addition, if there was recall bias, it seems unlikely that this systematically differed between the study groups. Therefore, we expect that this does not affect our estimations. A second limitation concerns the amount of incomplete data. Despite our efforts to obtain full data from the patients in the trial, only 70.4% of the study population had complete cost data. Although this is an acceptable rate of missing data, complete-case analyses may be biased and have less precision.[30, 31] We tried to account for this by applying multiple imputation for missing data.[32] Comparison of participants with complete and incomplete data resulted in a number of variables that predicted the presence of missing data. Therefore, we concluded that the data was missing at random, making multiple imputation the appropriate method to deal with the missing data. Finally, it should be noted that a typical feature of Internet-based interventions is the risk of selection bias towards the higher educated participant. Also in our study, included participant were employed women of which the majority was highly educated, and patients that were computer or Internet illiterate were excluded. Therefore, caution is needed when generalising the findings, as clinical and cost-effectiveness may be reduced when the intervention in accessible for the general audience. Moreover, due to (cultural) differences in attitudes towards health and work as well as differences in the organization of social and health care systems, generalisability of the results across countries might be hampered as well.

Comparison with other studies

We showed that costs associated with productivity loss following gynaecological surgery were about two times higher than healthcare costs. We are not aware of previously published literature in the gynaecological field in which this was demonstrated before. As a matter of fact, outcomes such as long-term convalescence, return to normal activities and absenteeism following gynaecological surgery are under-reported in clinical trials. In a review of Roumm et. al. assessing the clinical and economic benefits of minimal invasive surgery compared to open alternatives, only five of the 19 eligible studies reported data on return to work or return to normal activities, while 15 studies reported on hospital costs and all studies reported on

length of stay.[33] Similarly, in a recent Cochrane systematic review assessing the effectiveness and safety of different surgical approaches to hysterectomy in women with benign gynaecological disease, 45 of the 47 included studies reported on the length of postoperative hospital stay and only 19 studies reported data on return to normal activities.[34]

Cost-effectiveness is one of the most frequently cited reason for developing Internet interventions, because of the relative low delivery costs and the potential high impact.[35] However, economic evaluations are mainly lacking. A recent systematic review that evaluated the effect of perioperative e-Health interventions on the postoperative course, concluded that only 6 of 19 included studies reported on costs and in only one study a full economic evaluation was performed.[36] Thus, the current study addresses this literature gap as well.

Policy implications and recommendations

Whether the perioperative Internet-based care programme under study is considered cost-effective in comparison with usual care in accelerating return to work following gynaecological surgery depends on society's willingness to pay for a reduced sick leave day, as well as the probability of cost-effectiveness that is considered acceptable. Our results show that the probability of cost-effectiveness is 0.97 at a WTP of €76 per day earlier RTW. Considering that on average the costs of a day of sickness absence are €230,[18] we expect that this intervention can be considered cost-effective in comparison with usual care.

A latent barrier to future acceptance and implementation of the care programme lies in the fact that the costs and benefits of the care programme are separated between different types of stakeholders. In the Netherlands, medical costs are paid by the government and health insurance companies and sickness benefits are the main responsibility of the employers, which makes the shifting of costs across these sectors hard. As follows, investments are made in the healthcare sector for implementing the care programme and changing care processes, while the largest benefits accrue to employers through reduced lost productivity costs. However, many countries have an employer-provided health insurance (e.g. the United States), and in those countries this Internet-based care programme is much more likely to be adapted as investments in the Internet-based care programme may directly lead to savings through improved productivity rates.

Conclusions

The encouraging outcomes of this trial show that there is an economic case for supporting patients in the perioperative period with an Internet-based care programme. The care programme has a potential to lead to societal cost savings as a result of a reduction in the duration until full sustainable RTW. If society is willing to pay €76 per day earlier RTW, the care programme is considered cost-effective in comparison with usual care in women undergoing benign gynaecological surgery. Policy makers should investigate how these monetary benefits can be distributed across stakeholders.

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Contributorship statement

All named authors made substantial contributions to this study and the article. EVB, HAB, JRA, and JAH participated in the design and/or execution of the study, the interpretation of data, and the drafting and/or revision of the article. JEB and JMD were involved in the statistical data analyses and interpretation of the data, and the revision of the article. All named authors approved the final version of the manuscript. EVB and JAH are the study guarantors.

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Competing interests statement

All authors have completed the ICMJE uniform disclosure form at: www.icmje.org/coi_disclosure.pdf. Dr. Anema reports a chair in Insurance Medicine paid by the Dutch Social Security Agency, and he is stockholder of Evalua LTD. Dr. Huirne reports grants from Samsung, grants from Gideon Richter, grants from Celonova, outside the

submitted work. Dr. Brölmann reports grants from Olympus, personal fees from Nordic Farma, during the conduct of the study . Dr. Anema and dr. Huirne are planning to set up a spin-off company concerning the implementation of a mobile application concerning the IKHERSTEL intervention in the Netherlands. The remaining authors have nothing to disclose.

Ethics approval

The study protocol was approved by the Institutional Review Board of the VU University Medical Centre (16 May 2011, no. 2011/142) and by the medical ethics committees of all other participating Onze Lieve Vrouwe Gasthuis Oost (Amsterdam), Meander Medical Center (Amersfoort), Amstelland Hospital (Amsterdam), Medical Center Alkmaar (Alkmaar), Diakonessenhuis (Utrecht), Spaarne Gasthuis (locations Haarlem and Hoofddorp), and Flevo Hospital (Almere). Informed consent was obtained from all participants.

Data sharing

No additional data are available, though details on statistical analyses are available from the corresponding author on request.

Figure legends

Figure 1 Trial profile

No legend needed

Figure 2 Cost-effectiveness planes and cost-effectiveness acceptability curves for RTW and QALYs

Legend: The cost-effectiveness planes (a,c) indicate the uncertainty around the incremental cost-effectiveness ratio. The cost-effectiveness acceptability curves (b,d) indicate the probability of cost-effectiveness for different values (€) of willingness to pay per unit of effect gained. RTW, return to work; QALY, Quality Adjusted Life Year.

Supplementary files

Supplementary table S1 Costs of the intervention care programme from the societal perspective, valued using a bottom-up micro-costing approach.

Supplementary table S2 Differences in pooled means costs and effects, incremental cost-effectiveness ratios and the distribution of incremental cost-effectiveness pairs around the quadrants of the cost-effectiveness plane.

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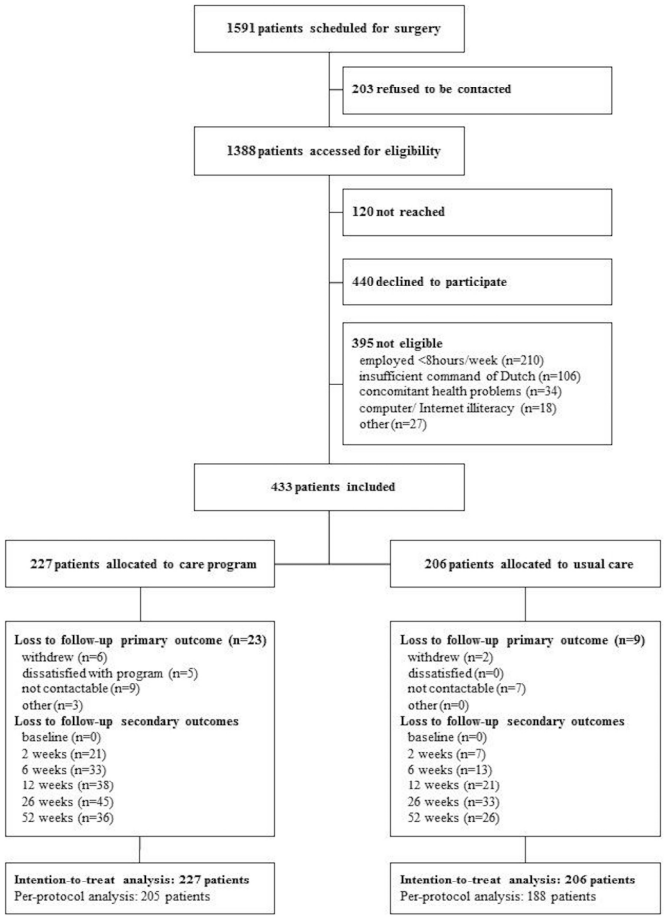

Figure 1 Trial profile

201x218mm (300 x 300 DPI)

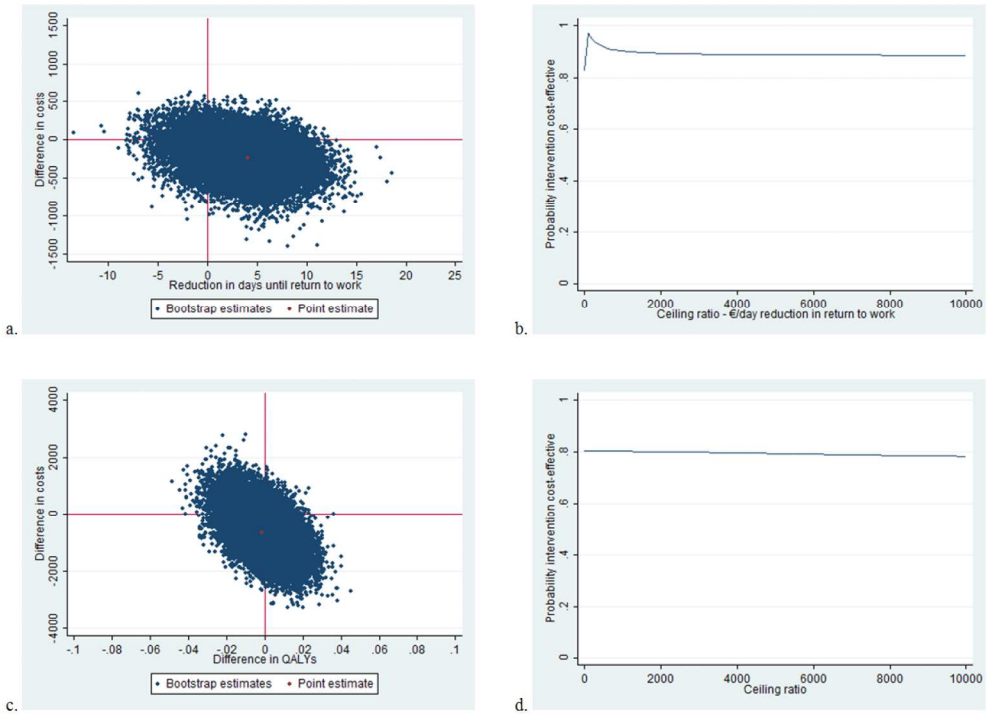

Figure 2 Cost-effectiveness planes and cost-effectiveness acceptability curves for RTW and QALYs. ‼ ┼ Legend: The cost-effectiveness planes (a,c) indicate the uncertainty around the incremental cost-effectiveness ratio. The cost-effectiveness acceptability curves (b,d) indicate the probability of cost-effectiveness for different values (€) of willingness to pay per unit of effect gained. RTW, return to work; QALY, Quality Adjusted Life Year.

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Supplementary table S1 Costs of the intervention care programme from the societal perspective, valued using a bottom-up micro-costing approach

Intervention component	Cost category	Staff	Units	Unit Price	Total costs (n=227)	Costs per patient
Implementation costs						
Training sessions	labour costs	principal investigator	5 hours	€ 36.94	€ 184.69	€ 0.81
(care-managers)	labour costs	occupational physicians	18 hours	€ 89.68	€ 1,614.24	€ 7.11
	labour costs	occupational therapist	2 hours	€ 46.32	€ 92.64	€ 0.41
	capital costs		5 hours	€ 6.26	€ 31.29	€ 0.14
Training sessions	labour costs	principal investigator	38 hours	€ 36.94	€ 1,403.67	€ 6.18
(hospital staff)	travel costs	principal investigator	582 km	€ 0.22	€ 127.28	€ 0.56
	labour costs	gynaecologists	18.9 hours	€ 107.30	€ 2,027.90	€ 8.93
	labour costs	residents	18.9 hours	€ 42.58	€ 804.82	€ 3.55
	labour costs	nurses	45 hours	€ 42.64	€ 1,918.58	€ 8.45
	capital costs		9 hours	€ 6.26	€ 56.33	€ 0.25
	printed materials				€ 821.00	€ 3.62
					Subtotal	**€ 40.01**
eHealth intervention						
Electronic approval	labour costs	gynaecologists	14.2 hours	€ 107.30	€ 1,523.60	€ 6.71
	capital costs		14.2 hours	€ 4.17	€ 59.15	€ 0.26
Maintenance	labour costs	computer specialist	12.2 hours	€ 37.82	€ 461.45	€ 2.03
	capital costs		12.2 hours	€ 1.67	€ 20.33	€ 0.09
Administrator time	labour costs	research assistant	37.8 hours	€ 33.42	€ 1,263.23	€ 5.56
	capital costs		37.8 hours	€ 4.17	€ 157.46	€ 0.69
Website hosting	other		40 months	€ 18.84	€ 578.88	€ 2.55
					Subtotal	**€ 17.90**
Occupational intervention						
Pre-operative consultations	labour costs	occupational physicians	7.9 hours	€ 89.68	€ 708.47	€ 3.12

	capital costs		7.9 hours	€ 4.17	€ 32.91	€ 0.14
	phone costs		413 minutes	€ 0.09	€ 38.71	€ 0.17
Post-operative consultations	labour costs	occupational physicians	37.5 hours	€ 89.68	€ 3.363.00	€ 14.81
	capital costs		37.5 hours	€ 4.17	€ 156.21	€ 0.69
	phone costs		2083 minutes	€ 0.09	€ 195.23	€ 0.86
Workplace intervention	labour costs	occupational therapist	4 hours	€ 46.32	€ 185.29	€ 0.82
	capital costs		3 hours	€ 6.26	€ 18.78	€ 0.08
	labour costs	employer	2 hours	€ 83.69	€ 167.37	€ 0.74
	travel costs	occupational therapist	110 km	€ 0.22	€ 24.06	€ 0.11
					Subtotal	**€ 21.54**
Developmental costs					€ 33,873.55	€ 0.56 [§]
					Subtotal	**€ 0.56**
TOTAL intervention costs						**€ 80.02**

Costs are expressed in 2014 Euros (€1.00 = £0.85; $1.06).

[§] € 33,873.55 was paid for the development of the intervention care-programme. For calculating the development costs per participant, these were divided by the expected number of users during the first five years after implementation (60,200). Per year 20,000 gynaecologic surgeries (LAS, TLH, VH, AH) are being performed in the Netherlands and based on the outcomes of an earlier performed process-evaluation we hypothesized a reach of 60.2%.[42]

Supplementary table S2 Differences in pooled means costs and effects, incremental cost-effectiveness ratios and the distribution of incremental cost-effectiveness pairs around the quadrants of the cost-effectiveness plane

Analysis	Sample size		Δ Cost* (€)	Δ Effect* (days)	ICER	Distribution CE-plane			
	IC	UC	mean (95% CI)	mean (95% CI)	€/day	NE[1]	SE[2]	SW[3]	NW[4]
QALYs									
Intention to treat	227	206	-647 (-2116 to 735)	-0.001 (-0.023 to 0.020)	501187	4%	42%	35%	19%
Per-protocol analysis	205	188	-1148 (-2611 to 162)	0.003 (-0.019 to 0.024)	-432881	1%	59%	34%	6%
Complete-case analysis	132	136	-1607 (-3421 to 52)	0.009 (-0.013 to 0.033)	-202816	1%	72%	24%	3%
Friction cost approach	227	206	-825 (-2209 to 470)	-0.001 (-0.023 to 0.020	639131	2%	44%	42%	12%
Healthcare perspective	227	206	-61 (-361 to 218)	-0.001 (-0.023 to 0.020	46942	13%	33%	28%	26%
SF-36 PHYSICAL COMPONENT SCORE									
Intention to treat	227	206	-647 (-2116 to 735)	-0.7 (-2.6 to 1.1)	870	6%	19%	58%	17%
Per-protocol analysis	205	188	-1148 (-2611 to 162)	-0.9 (-2.8 to 1.1)	1350	2%	21%	71%	6%
Complete-case analysis	153	149	-1689 (-3316 to -231)	-1.2 (-3.3 to 0.8)	1389	0%	12%	86%	2%
Friction cost approach	227	206	-825 (-2209 to 470)	-0.7 (-2.6 to 1.1)	1109	4%	21%	64%	11%
Healthcare perspective	227	206	-61 (-361 to 218)	-0.7 (-2.6 to 1.1)	81	8%	17%	44%	31%
SF-36 MENTAL COMPONENT SCALE									
Intention to treat	227	206	-647 (-2116 to 735)	-0.4 (-2.5 to 1.7)	1573	10%	33%	44%	13%
Per-protocol analysis	205	188	-1148 (-2611 to 162)	-0.5 (-2.7 to 1.7)	2198	2%	32%	61%	5%
Complete-case analysis	153	149	-1689 (-3316 to -231)	-0.1 (-2.6 to 1.9)	12598	1%	49%	49%	1%
Friction cost approach	227	206	-825 (-2209 to 470)	-0.4 (-2.5 to 1.7)	2006	6%	37%	49%	8%
Healthcare perspective	227	206	-61 (-361 to 218)	-0.4 (-2.5 to 1.7)	147	17%	26%	35%	22%
RECOVERY INDEX									
Intention to treat	227	206	-647 (-2116 to 735)	-0.6 (-2.0 to 0.9)	1127	5%	22%	55%	18%
Per-protocol analysis	205	188	-1148 (-2611 to 162)	-0.7 (-2.1 to 0.8)	1786	1%	23%	70%	6%
Complete-case analysis	153	149	-1689 (-3316 to -231)	-0.7 (-2.2 to 0.7)	2562	1%	20%	78%	1%
Friction cost approach	227	206	-825 (-2209 to 470)	-0.6 (-2.0 to 0.9)	1437	3%	24%	62%	12%
Healthcare perspective	227	206	-61 (-361 to 218)	-0.6 (-2.0 to 0.9)	106	8%	19%	42%	31%

* uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery

[1] Refers to the northeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and more costly than usual care.

[2] Refers to the southeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and less costly than usual care.

[3] Refers to the southwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and less costly than usual care.

[4] Refers to the northwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and more costly than usual care.

IC, intervention care; UC, usual care; ICER, Incremental Cost-effectiveness Ratio; CE plane, cost-effectiveness plane.

CHEERS checklist

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.	page 1, line 6.
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.	page 2, line 3 to 28.
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.	page 3, line 4 to 14; page 3, line 14 to 22.
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page 5, line 4 to 9; page 9, line 9 to 17.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page 4, line 33 to page 5, line 2.
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page 4, line 26 to 28.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	page 5, line 21 to page 6, line 9; page 6, line 11 to 18.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page 4, line 29 to 30; page 8, line 12 to 13.
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	page 8, line 12 to 13.
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.	page 6 , line 21 to 33.
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	page 4, line 25 to 28; page 5, line 22 to page 6, line 9.

Section/item	Item No	Recommendation	Reported on page No/line No
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	n/a
Estimating costs and resources	13a	*Single study-based economic evaluation*: 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.	page 7, line 1 to 24.
Currency, price date and conversion	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.	page 8, line 12 to 13; table 2.
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.	Page 8, line 25 to 32.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	page 8, line 18 to 23.
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.	page 8, line 18 to 23; page 9, line 1 to 7.
Results			
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.	page 10, line 1 to 19; table 2 and 3; table S1
Incremental costs and outcomes	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.	page 10, line 22 to page 11, line 12; table 4;
Characterising uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	page 11, line 14 to 23.

Section/item	Item No	Recommendation	Reported on page No/line No
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.	page 11, line 25 to page 12, line 12; page 13, line 19 to 27.
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.	page 12, line 14 to page 14, line 21; page 15, line 20 to 30.
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.	page 16, line 20 to 25.
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.	page 16, line 27 to page 17, line 2.

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Cost-effectiveness of an Internet-based perioperative care programme to enhance postoperative recovery in gynaecological patients: economic evaluation alongside a stepped-wedge cluster-randomised trial

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Title Page

Full title:

Cost-effectiveness of an Internet-based perioperative care programme to enhance postoperative recovery in gynaecological patients: economic evaluation alongside a stepped-wedge cluster-randomised trial

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Abstract

Objectives To evaluate the cost-effectiveness and cost-utility of an Internet-based perioperative care programme compared with usual care for gynaecological patients.

Design Economic evaluation from a societal perspective alongside a stepped-wedge cluster-randomised controlled trial with 12 months follow-up.

Setting Secondary care, nine hospitals in the Netherlands, 2011-2014.

Participants 433 employed women aged 18-65 scheduled for a hysterectomy and/or laparoscopic adnexal surgery.

Intervention The intervention comprised an Internet-based care programme aimed at improving convalescence and preventing delayed return to work following gynaecological surgery was sequentially rolled out. Depending on the implementation phase of their hospital, patients were allocated to usual care (n=206) or to the intervention (n=227).

Main outcome measures The primary outcome was duration until full sustainable return to work (RTW). Secondary outcomes were quality adjusted life years (QALYs), health-related quality of life and recovery.

Results At 12 months, there were no statistically significant differences in total societal costs (€-647; 95% CI €-2116 to €753) and duration until RTW (-4.1; 95% CI -10.8 to 2.6) between groups. The incremental cost-effectiveness ratio (ICER) for RTW was 56; each day earlier RTW in the intervention group was associated with cost savings of 56 euros compared to usual care. The probability of the intervention being cost-effective was 0.79 at a willingness-to-pay (WTP) of €0 per day earlier RTW, which increased to 0.97 at a WTP of €76 per day earlier RTW. The difference in QALYs gained over 12 months between the groups was clinically irrelevant resulting in a low probability of cost-effectiveness for QALYs.

Conclusions Considering that on average the costs of a day of sickness absence are €230, the care programme is considered cost-effective in comparison with usual care for duration until sustainable RTW after gynaecological surgery for benign disease. Future research should indicate whether widespread implementation of this care programme has the potential to reduce societal costs associated with gynaecological surgery.

Trial registration Netherlands National Trial Register NTR2933.

Key words gynaecology; Internet; telemedicine; self-management; convalescence; return to work; economic evaluation.

Strengths and limitations of this study

- This is the first economic evaluation on an Internet-based care programme aimed at improving convalescence and preventing delayed return to work following gynaecological surgery.
- The study was conducted alongside a cluster-randomised controlled trial allowing prospective collection of relevant cost and effect data.
- The study was performed from a societal perspective and costs associated with lost productivity included both absenteeism as well as presenteeism costs.
- A latent barrier to future acceptance and implementation of the care programme lies in the fact that the costs and benefits of the care programme are separated between different types of stakeholders.

Main document

Introduction

At present, there is a transition of perioperative care from the hospital setting towards the home environment.[1-4] The introduction of advanced surgical techniques in combination with the implementation of "fast-track" clinical pathways have considerably reduced the length of postoperative hospital stays and many (complex) surgeries are now being performed in an ambulatory setting.[5-7] This is beneficial from the perspective of the healthcare system, as it leads to the containment of healthcare costs.[1, 8]

However, costs associated with lost productivity following surgery contribute to the total societal costs of surgical procedures as well, and are mostly not taken into account. Moreover, there is considerable evidence that the duration of sick leave following gynaecological surgery generally exceeds the period considered appropriate by specialists.[9] Therefore, preventing unnecessary prolonged recovery following gynaecological surgery, may translate into considerable savings for society.

We developed an Internet-based care programme for patients undergoing gynaecological surgery for benign disease, aimed at facilitating recovery after discharge and preventing delayed return to work.[10, 11] In this paper, we report on the cost-effectiveness and cost-utility of the Internet-based care programme compared to usual care. The findings on clinical effectiveness were reported in a separate paper.

Methods

Study design and participants

This economic evaluation was performed from a societal perspective and was carried out alongside a stepped-wedge cluster randomised controlled trial comparing an Internet-based care programme with usual care for patients undergoing benign gynaecological surgery. The study was done in the Netherlands between October 2011 and July 2014. The follow-up period was 12 months. The trial protocol has been published previously in accordance to CONSORT extended guidelines.[9]

The clusters in this trial were formed by separate hospitals. A total of nine hospitals participated, which were selected before the start of the trial. Hospitals were eligible if they

performed at least 100 hysterectomies or laparoscopic adnexal surgeries annually, and were located within 50km of the VU medical centre, Amsterdam, the Netherlands.

Patients were recruited from the waiting lists for hysterectomy (abdominal, vaginal or laparoscopic) and laparoscopic adnexal surgery. Eligible participants were women aged 18-65 who were employed for at least eight hours a week (unpaid or paid employment, or self-employed). We excluded patients who had severe benign comorbidity, had a malignancy, were pregnant, were computer or Internet illiterate, were involved in a lawsuit against their employer, were on disability sick leave before surgery, or had insufficient command of Dutch.

Randomisation and blinding

Randomization took place at the level of the clusters and determined the order in which the intervention was implemented in the participating hospitals. The sequence was generated by a statistician using a computer generated list of random numbers. A stepped wedge approach was employed as it enabled us to study the implementation process as well.[9]

Patients, clinicians and researchers could not be blinded for the intervention. However, group allocation was concealed until patients had agreed to participate and provided written informed consent. Data analysts (EB, JB) were masked to group allocation.

Intervention care programme and implementation strategy

The development and content of the intervention care programme have been described elsewhere in more detail.[9, 11] A multi-faceted implementation strategy was employed to achieve maximal adoption of the care programme, targeting three different levels.

At the level of the organization, the structure of healthcare was changed by the introduction of the interactive web portal that was accessible for patients as well as their healthcare professionals. In addition, care managers were trained to help patients identify possible barriers to resuming work activities and could assist, if necessary, in the planning and execution of work resumption, before and after surgery.

At the level of the healthcare professional, educational training sessions were organised to introduce an earlier developed guideline on postoperative convalescence recommendations to stimulate evidence-based patient education.[10]

At the patient level, the care programme consisted of two steps. First, all participants allocated to the intervention group received access to the web portal several weeks prior to their surgery (eHealth intervention). The interactive web portal facilitated self-management by providing patients with individual tailored convalescence recommendations throughout the entire surgical pathway as well as monitoring recovery postoperatively through an interactive self-assessment tool. Second, for those patients at risk of prolonged sick leave, a care manager was available to provide additional guidance in the process of resuming work activities (occupational intervention).

Usual Care

Before the care programme was implemented in the hospitals, participating patients received usual care. Although considerable variation in usual care exists in the Netherlands, postoperative patients generally receive verbal instructions at discharge by a nurse and/or physician, sometimes accompanied by a letter or brochure. Usually, a postoperative consultation is planned six weeks after surgery. Due to Dutch legislation, employed patients who do not resume work within 6 weeks after the surgery are invited for a consultation with their occupational physician.

Main outcome measures

The primary outcome was duration until sustainable return to work (RTW) defined as the resumption of own work or other work with equal earnings, for at least 4 weeks without (partial or full) recurrence of sick leave. This definition was adopted as interventions aimed at expediting return to work of sick-listed employees should also aim at reducing recurrence of sickness absence in order to sustain employees at work after initial RTW. Data on return to work were collected by means of monthly electronic sick leave calendars.

Quality adjusted life years (QALYs) was one of the secondary outcomes and was measured using the Dutch version of the EuroQol five-dimensional questionnaire (EQ-5D-3L).[12] The Dutch tariff was used to estimate the utility of EQ-5D-3L health states.[13] QALYs were calculated by multiplying the utility with the amount of time a patient spent in a particular health state. Transitions between health states were linearly interpolated. Other secondary outcomes included health-related quality of life assessed by Short-Form Health Survey (SF-

36)[14], and recovery assessed by the Recovery Index (RI-10).[15] All secondary outcomes were assessed at baseline, and at 2, 6, 12, 26, and 52 weeks follow-up.

Service use and costs

The intervention and implementation strategy costs consisted of costs related to implementing the new care programme. A bottom-up micro-costing approach was used for estimating intervention costs, using detailed data regarding the quantity and unit prices of: (1) the training sessions of involved healthcare professionals (clinical staff, occupational physicians, occupational therapist), (2) the eHealth intervention (hosting of web portal, administrator time), and (3) the occupational intervention (number and duration of consultations).[16]

Data on healthcare services used and support received by the participants were collected using electronic questionnaires during one year. Each month, the patient was asked to report service use over the previous month. Patients who were not sick listed and did not have any healthcare costs during three consecutive months, received a shortened version of the questionnaire. In case of no response, electronic reminders were sent after one and two weeks. If participants did not respond to the electronic reminders either, an additional attempt was made to complete the missing data per email, mail or telephone every three months.

Only healthcare utilization and support related to the gynaecological surgery were collected, and included the following categories: surgery and initial hospitalization, primary and secondary care including complementary medicine, medication and medical aids, home care and informal help.

Service utilization was valued using Dutch standard costs.[17] If these were unavailable, prices according to professional organizations were used. The prices of prescribed drugs were estimated using the prices of the Royal Dutch Society for Pharmacy.[18]

Productivity Loss

Absenteeism costs were calculated using the Human Capital Approach (HCA). The net number of sick leave days during follow-up were multiplied by the estimated costs of one day of sick leave for females, stratified for age.[17] In case of partial sick leave, we assumed that participants were 100% productive during the hours of partial work resumption.

Presenteeism (i.e. reduced productivity while at work) was assessed monthly after full resumption of work using two items of the "Productivity and Disease Questionnaire" (PRODISQ).[19] Patients were asked to report the quantity (q1) and quality (q2) of the work performed during the latest day at work on an 11-point scale, ranging from "nothing/very bad quality" (0) to "same as normal"(10).

The level of presenteeism ($Pres_{day}$) on the latest day at work was calculated using the following formula: $Pres_{day} = (1-((q1*q2)/100))$.[19,20] Assuming linearity, the level of presenteeism on the latest day at work was then extrapolated over the total month. The total number of workdays lost due to presenteeism were calculated ($Pres_{month}$) by multiplying the participants' presenteeism level by their number of days worked during that month. Subsequently, presenteeism costs per month were calculated by multiplying $Pres_{month}$, by the estimated costs of one day of lost productivity.

The index year of the study was 2014. Discounting of costs was not necessary because the follow-up was one year.[21]

Statistical analysis

The sample size of the study (n=454) was calculated for detecting a relevant difference in return to work (hazard ratio (HR) of 1.5) in the main outcome study.[9] The economic evaluation was done according to the intention to treat principle. Missing cost and effect data during follow-up were imputed using multiple imputation by chained equations (MICE). Multiple imputation was done using SPSS 16.0 with predictive mean matching. An imputation model containing demographic and prognostic variables was used to create five complete datasets after which the loss of efficiency was smaller than 5%.[22] Rubin's rules were used to pool effects and costs from the five imputed datasets.[23]

Differences in costs and effects were estimated using linear multilevel regression analyses, while adjusting for type of surgery. Clustering at the hospital- and patient-level was accounted for in these multilevel models. For the cost-effectiveness and cost-utility analyses, we calculated incremental cost-effectiveness ratios (ICERs) by dividing the incremental costs by the incremental effects. The ICER indicates the additional investments needed for the intervention to gain one extra unit of effect compared with usual care. In the ICER for

duration until RTW, productivity costs due to sick leave were excluded from the cost estimates to avoid double counting.

We used non-parametric bootstrapping with 5000 replications to estimate 95% confidence intervals around cost differences and the uncertainty surrounding the ICERs.[24] To account for the clustering of data, bootstrap replications were stratified for hospital.[25] Bootstrapped cost-effect pairs were plotted on cost-effectiveness planes (CE planes) and used to estimate cost-effectiveness acceptability curves (CEA curves). CEA curves show the probability that a treatment is cost effective in comparison with the control treatment at a specific ceiling ratio, which is the amount of money society is willing to pay to gain one extra unit of effect.

Sensitivity analyses

To assess whether protocol deviations influenced the treatment effect, a per-protocol analysis was performed. In addition, to assess the robustness of the results, we carried out three sensitivity analyses. Firstly, we did a complete-case analysis to assess the cost-effectiveness of the interventions excluding patients who were lost to follow-up. Secondly, we replicated the cost-effectiveness analysis using the Friction Cost Approach. The FCA assumes that costs are limited to the friction period (i.e. the period needed to replace a sick worker). A friction period of 23 weeks and an elasticity of 0.8 was used. Thirdly, an analysis from the healthcare perspective was performed including only healthcare costs.

All statistical analyses followed a predefined analysis plan and were done in SPSS (version 16.0) and STATA (version 12SE).

Results

Participants

During the study period, 1591 patients were scheduled for a hysterectomy and/or laparoscopic adnexal surgery in the participating hospitals. In total, 433 patients enrolled in the study, 206 patients during the control phase and 227 patients during intervention phase (figure 1).

Participants' demographic and prognostic variables are presented in table 1. Complete follow-up data were obtained from 92.6% of the participants on the primary outcome RTW, from 71.8% on the secondary outcomes, and 70.0% on healthcare utilization. Baseline characteristics did not differ between participants with and without complete cost data, except

that patients with complete data on healthcare utilization used the Internet more frequently than women with incomplete data.

Table 1 Baseline characteristics of individual patients

	Care Programme (n=227)	Usual Care (n=206)
Patient characteristics		
Age (years ± SD)	46.1 ± 7.3	45.6 ± 6.7
Dutch nationality	220 (96.9%)	202 (98.1%)
Internet use (days/week)		
< 1	2 (0.9%)	3 (1.5%)
1 – 2	9 (4.0%)	10 (4.9%)
3 – 5	45 (19.8%)	42 (20.4%)
> 5	171 (75.3%)	151 (73.3%)
Education level *		
Low	25 (11.0%)	17 (8.3%)
Intermediate	88 (38.8%)	100 (48.5%)
High	114 (50.2%)	89 (43.2%)
Surgery-related characteristics		
Type of surgery		
Adnexal surgery	74 (32.6%)	51 (24.8%)
Laparoscopic hysterectomy	65 (28.6%)	50 (24.3%)
Vaginal hysterectomy	36 (15.9%)	53 (25.7%)
Abdominal hysterectomy	52 (22.9%)	52 (25.2%)
Health-related characteristics		
Perceived health status (mean ± SD)	75.8 ± 16.5	76.9 ± 16.7
Work-related characteristics		
Type of work		
Salary employed	194 (85.5%)	175 (85.0%)
Self-employed	28 (12.3%)	28 (13.6%)
Voluntary work	5 (2.2%)	3 (1.5%)
Work hours per week (mean ± SD)	29.7 ± 9.3	28.7 ± 8.2
Sick leave (3 months before surgery)		
Absence from work §	88 (38.8%)	66 (32.0%)
Number of sick leave days (median (IQR))	4.0 (2-10)	4.5 (2-11)
RTW expectation (long) †	42 (18.5%)	38 (18.4%)
RTW intention (low) ‡	45 (19.8%)	67 (32.5%)

Data are number of patients (%), unless otherwise indicated.
* Low=preschool, primary school; intermediate=secondary school; high=tertiary school, university, or postgraduate.
§ Defined as at least 1 day absence.
† Defined as expectation longer than 3 weeks for adnexal surgery, longer than 6 weeks for laparoscopic or vaginal hysterectomy, or longer than 8 weeks for abdominal hysterectomy.
‡ Defined as score 4 or 5 (range 1-5).
RTW, return to work.

Service use and costs

Table 2 presents the costs of self-reported service use per category over the 12 months of follow-up stratified by treatment group and the mean cost differences between both groups.

Intervention costs were €80 per participant (online supplementary table S1). Total societal costs per patient were €12,266 in the intervention group and €13,795 in the usual care group. After correction for clustering by hospital and adjustment for surgery type, total societal costs in the intervention group were €647 lower compared to the usual care group, but this difference was not statistically significant (95% CI €-2116 to €753). In both groups, costs related to productivity losses were about two times higher than total healthcare costs. There was no statistical significant differences in healthcare costs between the intervention group and usual care group (€-61; 95% CI €-361 to €218) and lost productivity costs (€-570; 95% CI €-1909 to €692). Only costs for secondary care were significantly lower in the intervention group compared to the usual care group (€-178; 95% CI €-400 to €-31).

Table 2 Costs associated with self-reported service used across treatment groups at 12 months follow-up

Cost category	Intervention mean (SEM) n=227	Usual care mean (SEM) n=206	Mean cost difference (95% CI)*
Healthcare costs	**3823 (99)**	**4142 (134)**	**-61 (-361 to 218)**
Surgery costs	3236 (64)	3413 (58)	34 (-118 to 174)
Primary care costs	179 (24)	167 (30)	14 (-58 to 95)
Secondary care costs	242 (42)	458 (98)	-178 (-400 to -31)
Costs of medication and aids	13 (4)	10 (4)	3 (-6 to 11)
Home help costs	72 (24)	94 (26)	-19 (-85 to 45)
Intervention	80 (0)	NA	80 (NA)
Lost productivity costs	**8443 (543)**	**9653 (528)**	**-570 (-1909 to 692)**
Costs of absenteeism from unpaid work	1845 (224)	2124 (299)	-144 (-756 to 282)
Costs of absenteeism from paid work	6499 (425)	7281 (344)	-424 (-1469 to 578)
Presenteeism costs	99 (78)	248 (127)	-154 (-458 to 82)
Total societal costs	**12266 (596)**	**13795 (602)**	**-647 (-2116 to 735)**

Costs are expressed in 2014 Euros (€1.00 = £0.85; $1.06).
Mean values summarize the costs derived after the imputation process.
* Uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery
SEM, standard error; CI, confidence interval; NA, not applicable.

Effectiveness

The mean duration until RTW in the intervention group was 49.6 days versus 56.2 days in the usual care group. The adjusted difference in duration until RTW between intervention and

usual care was -4.1 days, but this difference was not statistically significant (95% CI -10.8 to 2.6) (table 3). For the other outcomes, no statistically differences were found between both groups at 12 months either.

Table 3 Effects across treatment groups at 12 months follow-up

Outcomes	Intervention Mean (SEM) n=227	Usual care Mean (SEM) n=206	Mean effect difference (95% CI) *
Duration until RTW (days)	49.6 (2.7)	56.2 (2.2)	-4.1 (-10.8 to 2.6)
QALY's gained	0.96 (0.008)	0.96 (0.007)	-0.001 (-0.023 to 0.020)
HR-QoL (SF-36)			
PCS	5.7§ (0.7)	6.7§ (0.6)	-0.7 (-2.6 to 1.1)
MCS	3.3§ (0.7)	3.7§ (0.8)	-0.4 (-2.5 to 1.7)
Recovery (RI-10)	24.3§ (0.4)	25.0§ (0.5)	-0.6 (-2.0 to 0.9)

* Uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery.
§ Difference between baseline score and score at 12 months follow-up.
SEM, standard error; CI, confidence interval; RTW, return to work; QALY, Quality Adjusted Life Year; HR-QoL, health-related quality of life; SF, Short Form; PSC, physical component scale; MSC, mental component scale; RI, recovery index.

Cost-effectiveness

The results of the cost-effectiveness analysis for duration until RTW are presented in table 4. The incremental cost-effectiveness ratio (ICER) for sustainable RTW was 56 indicating that each day earlier RTW in the intervention group is associated with cost savings of 56 euros in comparison with the usual care group. In the cost-effectiveness plane, 69% of the incremental cost effect pairs were located in the south east quadrant indicating that the intervention is more effective and less costly than usual care (figure 2a). The cost-effectiveness acceptability curve presented in figure 2b shows that if the societal willingness-to-pay (WTP) for one earlier day of RTW is €0, the probability that the intervention is cost-effective in comparison with usual care is 0.79. This probability increases to 0.97 at max if the WTP is €76 per day earlier RTW.

As the differences observed for the outcomes health-related quality of life and recovery after 12 months were small and not significant, the ICERs for these outcomes were quite large. In the cost-effectiveness plane, the majority of cost-effect pairs were located in the southern quadrants, indicating the intervention was less expensive. However, the cost-effect pairs were roughly divided between the eastern and western quadrant indicating that the intervention can lead to both better and worse outcomes compared to usual care (figure 2c).

Table 4 Differences in pooled means costs and effects, incremental cost-effectiveness ratios and the distribution of incremental cost-effectiveness pairs around the quadrants of the cost-effectiveness planes (main analysis)

Outcome	**Δ Cost*** (€) mean (95% CI)	**Δ Effect*** (days) mean (95% CI)	**ICER** €/day	**Distribution CE-plane**			
				NE[1]	**SE[2]**	**SW[3]**	**NW[4]**
RTW	-228 (-708 to 136)	4.1[§] (-2.6 to 10.8)	-56	15%	69%	10%	6%
QALY's gained	-647 (-2116 to 735)	-0.001 (-0.023 to 0.020)	501187	4%	42%	35%	19%
HR-QoL (SF36)							
PCS	-647 (-2116 to 735)	-0.7 (-2.6 to 1.1)	870	6%	19%	58%	17%
MCS	-647 (-2116 to 735)	-0.4 (-2.5 to 1.7)	1573	10%	33%	44%	13%
Recovery (RI-10)	-647 (-2116 to 735)	-0.6 (-2.0 to 0.9)	1127	5%	22%	55%	18%

* uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery

[§] Note that a positive value indicates faster RTW in the intervention group compared to the control group.

[1] Refers to the northeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and more costly than usual care.

[2] Refers to the southeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and less costly than usual care.

[3] Refers to the southwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and less costly than usual care.

[4] Refers to the northeast quadrant of the CE-plane, indicating that the intervention care programme is less effective and more costly than usual care.

ICER, Incremental Cost-Effectiveness Ratio; CE plane, cost-effectiveness plane; RTW, return to work; QALY, Quality Adjusted Life Year; HR-QoL, health-related quality of life; SF, Short Form; PSC, physical component scale; MSC, mental component scale; RI, recovery index.

Table 5 Results from the per-protocol and sensitivity analyses (Return to Work)

Analysis	**Sample size**		**Δ Cost*** (€)	**Δ Effect*** (days)	**ICER**	**Distribution CE-plane**			
	IC	**UC**	mean (95% CI)	mean (95% CI)	€/day	**NE[1]**	**SE[2]**	**SW[3]**	**NW[4]**
Per-protocol analysis	205	188	-359 (-866 to -11)	6.4[§] (-0.2 to 12.9)	-56	8%	87%	5%	1%
Complete-case analysis	154	150	-45 (-466 to 362)	11.6[§] (-5.4 to 19.3)	-4	45%	55%	0%	0%
Friction cost approach	227	206	-228 (-708 to 136)	4.1[§] (-2.6 to 10.8)	-56	15%	69%	10%	6%
Healthcare perspective	227	206	-61 (-361 to 218)	4.1[§] (-2.6 to 10.8)	-15	28%	56%	5%	10%

* uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery

[§] Note that a positive value indicates faster RTW in the intervention group compared to the control group.

[1] Refers to the northeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and more costly than usual care.

[2] Refers to the southeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and less costly than usual care.

[3] Refers to the southwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and less costly than usual care.

[4] Refers to the northwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and more costly than usual care.

IC, intervention care; UC, usual care; ICER, Incremental Cost-Effectiveness Ratio; CE plane, cost-effectiveness plane.

Cost-utility

The difference in QALYs gained over 12 months between the two study groups was small and not statistically significant or clinically relevant (table 4). Therefore, the ICER for QALYs became extraordinary large (half million Euros). As a result, the probability that the intervention was cost-effective in comparison with usual care was considerably lower than for the primary outcome (0.77 at WTP is €0 per QALY gained and decreasing at higher WTP values) (figure 2d).

Per-protocol analysis

In the per-protocol analysis 40 patients were excluded because they did not receive the care according to protocol due to several reasons: did not fit the inclusion criteria (n=3); had a more severe surgery than planned (n=25), or had a complicated postoperative course and needed a repeat surgery during follow-up (n=12). By excluding those patients, the difference in effect became larger, but was still not significant (-6.4 days, 95% CI -12.9 to 0.20) and the cost differences became statistically significant in favour of the intervention (mean difference €-359, 95% CI -866 to -11) (table 5). Hence, compared to the main analysis, the probability of cost-effectiveness increased considerably at a WTP of €0 per one day earlier RTW (from 0.79 to 0.92).

Sensitivity analyses

The results of the primary outcome in the sensitivity analyses differed in some aspects from the main analysis (table 5). First, in the complete-case analysis, the effect difference between study groups became larger in favour of the intervention group, but the cost savings in the intervention group as compared to usual care became smaller. The probability of cost-effectiveness compared to the main analysis therefore decreased (from 0.79 to 0.55). Second, in the analyses performed from the healthcare perspective, cost savings became much smaller, as costs associated with lost productivity were not taken into account. As a result the probability of cost-effectiveness reduced (from 0.79 to 0.61). Finally, the results from the friction cost analysis were identical to the intention to treat analysis, indicating that the majority of patients returned to their work before the end of the friction period of 23 weeks.

The results of the per-protocol analyses and sensitivity analyses for the secondary outcomes QALYs, health-related quality of life and recovery are presented in online supplementary table S2. In the per-protocol analyses, cost differences became larger in favour of the

intervention group, however, they did not reach statistical significance. The probability of cost-effectiveness at a WTP of €0 per unit of effect increased from 0.77 to 0.93. In contrast to the complete-case analysis for the primary outcome, the complete-case analyses for the secondary outcomes showed a statistical significant increase in cost savings in the intervention group. The probability of cost-effectiveness at a WTP of €0 per unit of effect increased from 0.77 to 0.98

Discussion

In this study, we evaluated the cost-effectiveness and cost-utility of a rigorously designed Internet-based perioperative care programme compared with usual care for gynaecological patients. Our results show that for the primary outcome duration until full resumption of work, the probability that the care programme is cost-effective as compared to usual care is 0.97 at a willingness to pay of €76 per day earlier RTW. Taking into account that the average costs per sick leave day are €230, we conclude that the intervention is cost-effective as compared to usual care.

Interpretation of the findings

In the current economic evaluation, the adjusted mean difference until RTW between study groups was not statistically significant (-4.1 days, 95% CI -10.8 to 2.6). In the accompanying paper on the clinical effectiveness of the intervention, median days until RTW were compared between study arms using Cox regression analyses. However, survival analysis results in difficulties in interpreting the ICER. Therefore, we chose to compare mean days until RTW in the current cost-effectiveness study and used bootstrapping to account for the skewed distribution of this variable.

In addition, the cost-difference between the intervention group and the control group was not statistically significant either, although total societal costs were lower in the intervention group than in the control group. A possible explanation might be that the sample size of this study was based on the primary outcome full sustainable return to work, and, therefore, underpowered to detect relevant cost differences, as cost data are right skewed and require relative large samples.[26]

Secondary care costs in the intervention group were lower compared to the usual care group. Future research should investigate if the care programme truly leads to different health

seeking behaviour. Possibly, patients receiving additional perioperative care were more confident in their own self-management skills preventing them from visiting a healthcare professional. In addition, costs associated with primary care were similar in both groups, demonstrating that the care programme did not cause a shift from secondary care to primary care in the intervention group compared to the usual care group. Concerns of increased workload in the primary care setting due to changes in perioperative care have been reported before, however, seem to be ungrounded.[27, 28]

We did not find any clinical relevant differences in the secondary outcomes. Thus, despite the possible difference in the RTW rates between study groups, this did not have an effect on patients' perceptions about their quality of life and recovery. Possibly, the surgery itself has a much larger impact on these outcomes than the method of postoperative guidance.

The results of the per-protocol analyses, were slightly more favourable than those of the main analyses. Thus, by presenting the intervention to the ideal target population, the probability of cost-effectiveness of the intervention in comparison with usual care increases. This is in concordance with our initial objective to develop Internet-based care programme for women undergoing an uncomplicated surgical procedure.[10] It may be challenging to identify future patients who will benefit most from the care programme, as complications cannot always be predicted pre-operatively. In addition, it should be investigated further what the needs are of patients with a complicated course and how they should best be guided and monitored during their recovery.

Strengths and weaknesses of the study

Several strengths of the present study are noteworthy. First of all, we are not aware of other current perioperative interventions that aim at preventing unnecessary prolonged recovery and reducing sick leave in order to contain societal costs associated with gynaecological surgical care. Second, analyses were performed alongside a pragmatic trial, allowing prospective collection of relevant cost and effect data and enabling the evaluation of the intervention's cost-effectiveness under real world conditions.[26] The third strength concerns the use of linear multilevel analyses to account for possible clustering of data as a result of the chosen study design. Randomization at cluster level was chosen to prevent contamination between the study arms. Moreover, the employment of a stepped wedge design allowed the sequential

implementation of the care programme in the participating hospitals, providing the possibility to study the implementation process as well.

Our study also has limitations. The first limitation is the collection of cost data through self-reported retrospective questionnaires. However, since administrative data on service use are very hard to obtain in the Netherlands, societal cost data can only be collected by means of self-report. In order to prevent recall-bias, we minimised the recall period to only one month. In addition, if there was recall bias, it seems unlikely that this systematically differed between the study groups. Therefore, we expect that this does not affect our estimations. A second limitation concerns the amount of incomplete data. Despite our efforts to obtain full data from the patients in the trial, only 70.4% of the study population had complete cost data. Although this is an acceptable rate of missing data, complete-case analyses may be biased and have less precision.[29, 30] We tried to account for this by applying multiple imputation for missing data.[31] Comparison of participants with complete and incomplete data resulted in a number of variables that predicted the presence of missing data. Therefore, we concluded that the data was missing at random, making multiple imputation the appropriate method to deal with the missing data. Finally, it should be noted that a typical feature of Internet-based interventions is the risk of selection bias towards the higher educated participant. Also in our study, included participant were employed women of which the majority was highly educated, and patients that were computer or Internet illiterate were excluded. Therefore, caution is needed when generalising the findings, as clinical and cost-effectiveness may be reduced when the intervention in accessible for the general audience. Moreover, due to (cultural) differences in attitudes towards health and work as well as differences in the organization of social and health care systems, generalisability of the results across countries might be hampered as well.

Comparison with other studies

We showed that costs associated with productivity loss following gynaecological surgery were about two times higher than healthcare costs. We are not aware of previously published literature in the gynaecological field in which this was demonstrated before. As a matter of fact, outcomes such as long-term convalescence, return to normal activities and absenteeism following gynaecological surgery are under-reported in clinical trials. In a review of Roumm et. al. assessing the clinical and economic benefits of minimal invasive surgery compared to open alternatives, only five of the 19 eligible studies reported data on return to work or return to normal activities, while 15 studies reported on hospital costs and all studies reported on

length of stay.[32] Similarly, in a recent Cochrane systematic review assessing the effectiveness and safety of different surgical approaches to hysterectomy in women with benign gynaecological disease, 45 of the 47 included studies reported on the length of postoperative hospital stay and only 19 studies reported data on return to normal activities.[33]

Cost-effectiveness is one of the most frequently cited reason for developing Internet interventions, because of the relative low delivery costs and the potential high impact.[34] However, economic evaluations are mainly lacking. A recent systematic review that evaluated the effect of perioperative e-Health interventions on the postoperative course, concluded that only 6 of 19 included studies reported on costs and in only one study a full economic evaluation was performed.[35] Thus, the current study addresses this literature gap as well.

Policy implications and recommendations

Whether the perioperative Internet-based care programme under study is considered cost-effective in comparison with usual care in accelerating return to work following gynaecological surgery depends on society's willingness to pay for a reduced sick leave day, as well as the probability of cost-effectiveness that is considered acceptable. Our results show that the probability of cost-effectiveness is 0.97 at a WTP of €76 per day earlier RTW. Considering that on average the costs of a day of sickness absence are €230,[17] we expect that this intervention can be considered cost-effective in comparison with usual care.

A latent barrier to future acceptance and implementation of the care programme lies in the fact that the costs and benefits of the care programme are separated between different types of stakeholders. In the Netherlands, medical costs are paid by the government and health insurance companies and sickness benefits are the main responsibility of the employers, which makes the shifting of costs across these sectors hard. As follows, investments are made in the healthcare sector for implementing the care programme and changing care processes, while the largest benefits accrue to employers through reduced lost productivity costs. However, many countries have an employer-provided health insurance (e.g. the United States), and in those countries this Internet-based care programme is much more likely to be adapted as investments in the Internet-based care programme may directly lead to savings through improved productivity rates.

Conclusions

The encouraging outcomes of this trial show that there is an economic case for supporting patients in the perioperative period with an Internet-based care programme. The care programme has a potential to lead to societal cost savings as a result of a reduction in the duration until full sustainable RTW. If society is willing to pay €76 per day earlier RTW, the care programme is considered cost-effective in comparison with usual care in women undergoing benign gynaecological surgery. Policy makers should investigate how these monetary benefits can be distributed across stakeholders.

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Contributorship statement

All named authors made substantial contributions to this study and the article. EVB, HAB, JRA, and JAH participated in the design and/or execution of the study, the interpretation of data, and the drafting and/or revision of the article. JEB and JMD were involved in the statistical data analyses and interpretation of the data, and the revision of the article. All named authors approved the final version of the manuscript. EVB and JAH are the study guarantors.

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Competing interests statement

All authors have completed the ICMJE uniform disclosure form at: www.icmje.org/coi_disclosure.pdf. Dr. Anema reports a chair in Insurance Medicine paid by the Dutch Social Security Agency, and he is stockholder of Evalua LTD. Dr. Huirne reports grants from Samsung, grants from Gideon Richter, grants from Celonova, outside the

submitted work. Dr. Brölmann reports grants from Olympus, personal fees from Nordic Farma, during the conduct of the study . Dr. Anema and dr. Huirne are planning to set up a spin-off company concerning the implementation of a mobile application concerning the IKHERSTEL intervention in the Netherlands. The remaining authors have nothing to disclose.

Ethics approval

The study protocol was approved by the Institutional Review Board of the VU University Medical Centre (16 May 2011, no. 2011/142) and by the medical ethics committees of all other participating Onze Lieve Vrouwe Gasthuis Oost (Amsterdam), Meander Medical Center (Amersfoort), Amstelland Hospital (Amsterdam), Medical Center Alkmaar (Alkmaar), Diakonessenhuis (Utrecht), Spaarne Gasthuis (locations Haarlem and Hoofddorp), and Flevo Hospital (Almere). Informed consent was obtained from all participants.

Data sharing

No additional data are available, though details on statistical analyses are available from the corresponding author on request.

Figure legends

Figure 1 Trial profile

No legend needed

Figure 2 Cost-effectiveness planes and cost-effectiveness acceptability curves for RTW and QALYs

Legend: The cost-effectiveness planes indicate the uncertainty around the incremental cost-effectiveness ratio for RTW (a) and QALYs (c). The cost-effectiveness acceptability curves indicate the probability of cost-effectiveness for different values (€) of willingness to pay per unit of effect gained for RTW (b) and QALYs (d).

RTW, return to work; QALY, Quality Adjusted Life Year.

Supplementary files

Supplementary table S1 Costs of the intervention care programme from the societal perspective, valued using a bottom-up micro-costing approach.

Supplementary table S2 Differences in pooled means costs and effects, incremental cost-effectiveness ratios and the distribution of incremental cost-effectiveness pairs around the quadrants of the cost-effectiveness plane.

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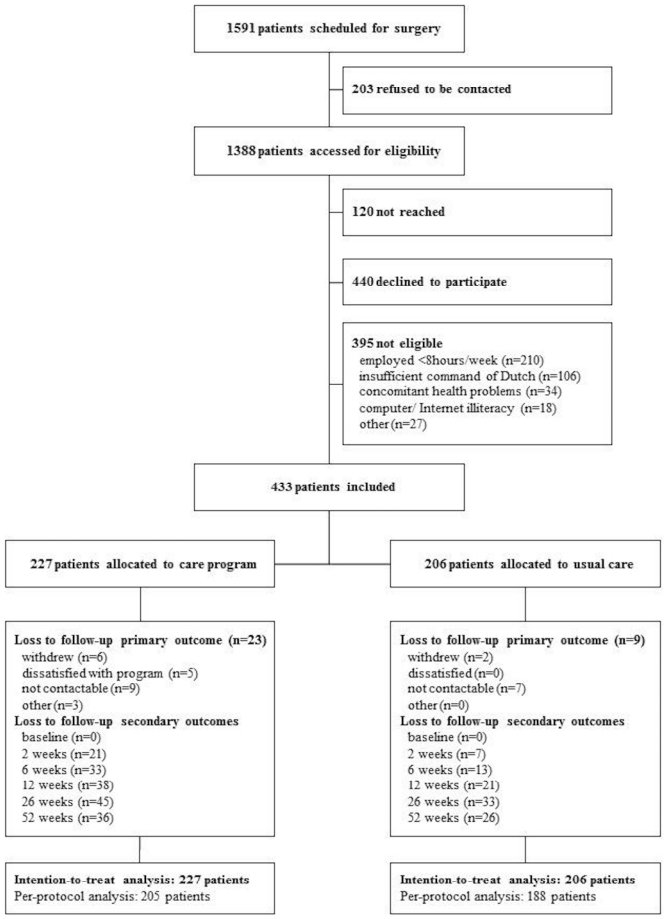

Figure 1 Trial profile

201x218mm (300 x 300 DPI)

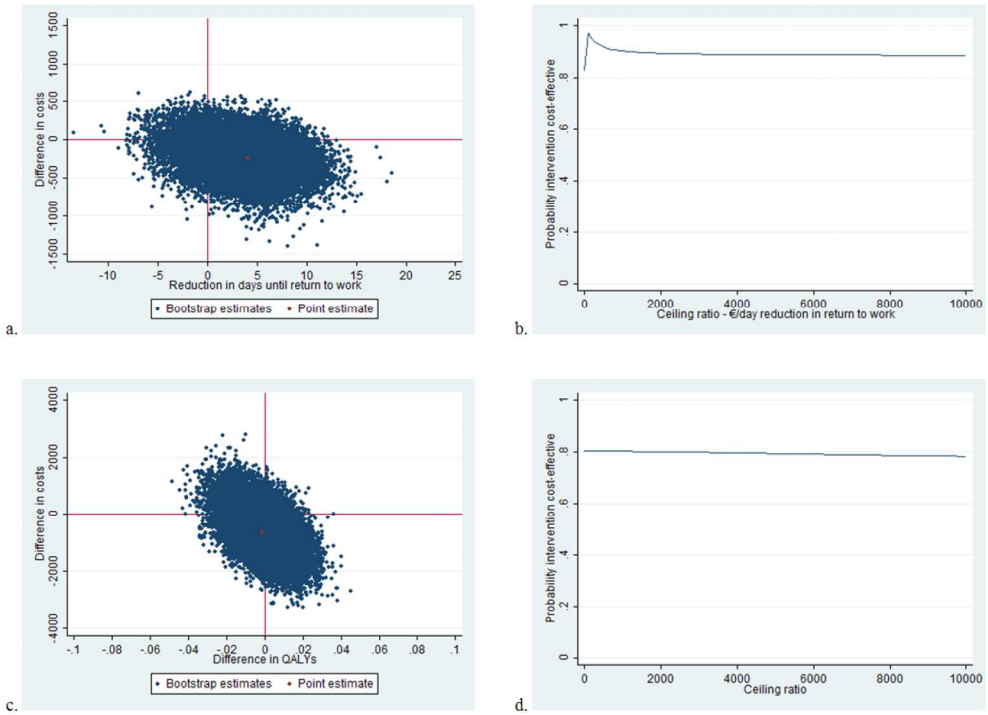

Figure 2 The cost-effectiveness planes indicate the uncertainty around the incremental cost-effectiveness ratio for RTW (a) and QALYs (c). The cost-effectiveness acceptability curves indicate the probability of cost-effectiveness for different values (€) of willingness to pay per unit of effect gained for RTW (b) and QALYs (d).
RTW, return to work; QALY, Quality Adjusted Life Year.

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Supplementary table S1 Costs of the intervention care programme from the societal perspective, valued using a bottom-up micro-costing approach

Intervention component	Cost category	Staff	Units	Unit Price	Total costs (n=227)	Costs per patient
Implementation costs						
Training sessions	labour costs	principal investigator	5 hours	€ 36.94	€ 184.69	€ 0.81
(care-managers)	labour costs	occupational physicians	18 hours	€ 89.68	€ 1,614.24	€ 7.11
	labour costs	occupational therapist	2 hours	€ 46.32	€ 92.64	€ 0.41
	capital costs		5 hours	€ 6.26	€ 31.29	€ 0.14
Training sessions	labour costs	principal investigator	38 hours	€ 36.94	€ 1,403.67	€ 6.18
(hospital staff)	travel costs	principal investigator	582 km	€ 0.22	€ 127.28	€ 0.56
	labour costs	gynaecologists	18.9 hours	€ 107.30	€ 2,027.90	€ 8.93
	labour costs	residents	18.9 hours	€ 42.58	€ 804.82	€ 3.55
	labour costs	nurses	45 hours	€ 42.64	€ 1,918.58	€ 8.45
	capital costs		9 hours	€ 6.26	€ 56.33	€ 0.25
	printed materials				€ 821.00	€ 3.62
					Subtotal	**€ 40.01**
eHealth intervention						
Electronic approval	labour costs	gynaecologists	14.2 hours	€ 107.30	€ 1,523.60	€ 6.71
	capital costs		14.2 hours	€ 4.17	€ 59.15	€ 0.26
Maintenance	labour costs	computer specialist	12.2 hours	€ 37.82	€ 461.45	€ 2.03
	capital costs		12.2 hours	€ 1.67	€ 20.33	€ 0.09
Administrator time	labour costs	research assistant	37.8 hours	€ 33.42	€ 1,263.23	€ 5.56
	capital costs		37.8 hours	€ 4.17	€ 157.46	€ 0.69
Website hosting	other		40 months	€ 18.84	€ 578.88	€ 2.55
					Subtotal	**€ 17.90**
Occupational intervention						
Pre-operative consultations	labour costs	occupational physicians	7.9 hours	€ 89.68	€ 708.47	€ 3.12

	capital costs		7.9 hours	€ 4.17	€ 32.91	€ 0.14
	phone costs		413 minutes	€ 0.09	€ 38.71	€ 0.17
Post-operative consultations	labour costs	occupational physicians	37.5 hours	€ 89.68	€ 3.363.00	€ 14.81
	capital costs		37.5 hours	€ 4.17	€ 156.21	€ 0.69
	phone costs		2083 minutes	€ 0.09	€ 195.23	€ 0.86
Workplace intervention	labour costs	occupational therapist	4 hours	€ 46.32	€ 185.29	€ 0.82
	capital costs		3 hours	€ 6.26	€ 18.78	€ 0.08
	labour costs	employer	2 hours	€ 83.69	€ 167.37	€ 0.74
	travel costs	occupational therapist	110 km	€ 0.22	€ 24.06	€ 0.11
					Subtotal	**€ 21.54**
Developmental costs					€ 33,873.55	€ 0.56 [§]
					Subtotal	**€ 0.56**
TOTAL intervention costs						**€ 80.02**

Costs are expressed in 2014 Euros (€1.00 = £0.85; $1.06).

[§] € 33,873.55 was paid for the development of the intervention care-programme. For calculating the development costs per participant, these were divided by the expected number of users during the first five years after implementation (60,200). Per year 20,000 gynaecologic surgeries (LAS, TLH, VH, AH) are being performed in the Netherlands and based on the outcomes of an earlier performed process-evaluation we hypothesized a reach of 60.2%.[42]

Supplementary table S2 Differences in pooled means costs and effects, incremental cost-effectiveness ratios and the distribution of incremental cost-effectiveness pairs around the quadrants of the cost-effectiveness plane

Analysis	Sample size		Δ Cost* (€)	Δ Effect* (days)	ICER	Distribution CE-plane			
	IC	UC	mean (95% CI)	mean (95% CI)	€/day	NE[1]	SE[2]	SW[3]	NW[4]
QALYs									
Intention to treat	227	206	-647 (-2116 to 735)	-0.001 (-0.023 to 0.020)	501187	4%	42%	35%	19%
Per-protocol analysis	205	188	-1148 (-2611 to 162)	0.003 (-0.019 to 0.024)	-432881	1%	59%	34%	6%
Complete-case analysis	132	136	-1607 (-3421 to 52)	0.009 (-0.013 to 0.033)	-202816	1%	72%	24%	3%
Friction cost approach	227	206	-825 (-2209 to 470)	-0.001 (-0.023 to 0.020	639131	2%	44%	42%	12%
Healthcare perspective	227	206	-61 (-361 to 218)	-0.001 (-0.023 to 0.020	46942	13%	33%	28%	26%
SF-36 PHYSICAL COMPONENT SCORE									
Intention to treat	227	206	-647 (-2116 to 735)	-0.7 (-2.6 to 1.1)	870	6%	19%	58%	17%
Per-protocol analysis	205	188	-1148 (-2611 to 162)	-0.9 (-2.8 to 1.1)	1350	2%	21%	71%	6%
Complete-case analysis	153	149	-1689 (-3316 to -231)	-1.2 (-3.3 to 0.8)	1389	0%	12%	86%	2%
Friction cost approach	227	206	-825 (-2209 to 470)	-0.7 (-2.6 to 1.1)	1109	4%	21%	64%	11%
Healthcare perspective	227	206	-61 (-361 to 218)	-0.7 (-2.6 to 1.1)	81	8%	17%	44%	31%
SF-36 MENTAL COMPONENT SCALE									
Intention to treat	227	206	-647 (-2116 to 735)	-0.4 (-2.5 to 1.7)	1573	10%	33%	44%	13%
Per-protocol analysis	205	188	-1148 (-2611 to 162)	-0.5 (-2.7 to 1.7)	2198	2%	32%	61%	5%
Complete-case analysis	153	149	-1689 (-3316 to -231)	-0.1 (-2.6 to 1.9)	12598	1%	49%	49%	1%
Friction cost approach	227	206	-825 (-2209 to 470)	-0.4 (-2.5 to 1.7)	2006	6%	37%	49%	8%
Healthcare perspective	227	206	-61 (-361 to 218)	-0.4 (-2.5 to 1.7)	147	17%	26%	35%	22%
RECOVERY INDEX									
Intention to treat	227	206	-647 (-2116 to 735)	-0.6 (-2.0 to 0.9)	1127	5%	22%	55%	18%
Per-protocol analysis	205	188	-1148 (-2611 to 162)	-0.7 (-2.1 to 0.8)	1786	1%	23%	70%	6%
Complete-case analysis	153	149	-1689 (-3316 to -231)	-0.7 (-2.2 to 0.7)	2562	1%	20%	78%	1%
Friction cost approach	227	206	-825 (-2209 to 470)	-0.6 (-2.0 to 0.9)	1437	3%	24%	62%	12%
Healthcare perspective	227	206	-61 (-361 to 218)	-0.6 (-2.0 to 0.9)	106	8%	19%	42%	31%

* uncertainty estimated using bootstrapping and corrected for clustering by hospital and type of surgery

[1] Refers to the northeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and more costly than usual care.

[2] Refers to the southeast quadrant of the CE-plane, indicating that the intervention care programme is more effective and less costly than usual care.

[3] Refers to the southwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and less costly than usual care.

[4] Refers to the northwest quadrant of the CE-plane, indicating that the intervention care programme is less effective and more costly than usual care.

IC, intervention care; UC, usual care; ICER, Incremental Cost-effectiveness Ratio; CE plane, cost-effectiveness plane.

CHEERS checklist

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.	page 1, line 6.
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.	page 2, line 3 to 28.
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.	page 3, line 4 to 14; page 3, line 14 to 22.
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page 5, line 4 to 9; page 9, line 9 to 17.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	page 4, line 33 to page 5, line 2.
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page 4, line 26 to 28.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	page 5, line 21 to page 6, line 9; page 6, line 11 to 18.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page 4, line 29 to 30; page 8, line 12 to 13.
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	page 8, line 12 to 13.
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.	page 6 , line 21 to 33.
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	page 4, line 25 to 28; page 5, line 22 to page 6, line 9.

Section/item	Item No	Recommendation	Reported on page No/line No
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	n/a
Estimating costs and resources	13a	*Single study-based economic evaluation*: 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.	page 7, line 1 to 24.
Currency, price date and conversion	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.	page 8, line 12 to 13; table 2.
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.	Page 8, line 25 to 32.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	page 8, line 18 to 23.
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.	page 8, line 18 to 23; page 9, line 1 to 7.
Results			
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.	page 10, line 1 to 19; table 2 and 3; table S1
Incremental costs and outcomes	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.	page 10, line 22 to page 11, line 12; table 4;
Characterising uncertainty	20a	*Single study-based economic evaluation*: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	page 11, line 14 to 23.

Section/item	Item No	Recommendation	Reported on page No/line No
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.	page 11, line 25 to page 12, line 12; page 13, line 19 to 27.
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.	page 12, line 14 to page 14, line 21; page 15, line 20 to 30.
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.	page 16, line 20 to 25.
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.	page 16, line 27 to page 17, line 2.