

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of an Internet-based perioperative care programme to enhance postoperative recovery in gynaecological patients: cluster controlled trial with randomised stepped-wedge implementation
AUTHORS	Bouwsma, Esther; Huirne, Judith; van de Ven, Peter; Vonk Noordegraaf, Antonie; Schaafsma, F; Schraffordt Koops, Steven; van Kesteren, Paul; Brölmann, Hans; Anema, Johannes

VERSION 1 – REVIEW

REVIEWER	Thomas Poder CIUSSS de l'Estrie - CHUS
REVIEW RETURNED	26-May-2017

GENERAL COMMENTS	<p>I reviewed the manuscript entitled "Effectiveness of an Internet-based perioperative care programme to enhance postoperative recovery in gynaecological patients: cluster controlled trial with randomised stepped-wedge implementation". In the document provided by BMJ Open, two other manuscripts were included: one is a protocol and the other one is a cost-effectiveness analysis. I did not review these two manuscripts.</p> <p>I consider that the manuscript "Effectiveness of an Internet-based perioperative care programme to enhance postoperative recovery in gynaecological patients: cluster controlled trial with randomised stepped-wedge implementation" is a well done study and I have no major comments to provide. Specifically, BMJ Open asked me to review the statistical methods. The methods used are very appropriate and I have no concern. This was very well done. Thanks.</p>
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REVIEWER	John Harris University of Pittsburgh USA
REVIEW RETURNED	01-Jun-2017

GENERAL COMMENTS	<p>The authors present a cluster controlled trial with randomized stepped-wedge implementation of a perioperative care program designed to quicken full return to work (RTW after hysterectomy). They found that the intervention helped patients to RTW in less than 85 days (HR 2.66, 1.88-3.77).</p> <p>Quicker postoperative return to full activities and work is an issue that is of interest to all surgical, public health, and economic specialists globally.</p>
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This rigorous implementation of an RCT-proven intervention is a model for this sort of implementation research in gynecology and surgical research in general. The research design, methodology, and analysis plan is high-quality. The improvement in time interval to RTW of 13 days is an impressive effect for patients, policy makers, and employers.

My only criticism pertains to ensuring that this work is clearly described to a general audience.

1. The title does not clearly describe the goal of intervention—to decrease time to full, sustained work activity. Instead of an “Internet-based perioperative care programme to enhance postoperative recovery”, I might suggest “a personalized, internet-based programme for expedient return to full work activities” or something that clearly describes the ultimate goal.

2. In the main outcome measures, “Indicators at the level of the patient, the healthcare provider and the organisation were used to measure the degree of implementation of the programme” sentence should be modified to clearly show that this involved an audit of internet-based actions by patients and providers.

3. In the abstract, I found this important sentence confusing: “Duration to RTW was effectively reduced in the first 85 days after surgery (hazard ratio 2.66, 95% CI 1.88 to 3.77), but the effect was reversed in the small group of patients that did not return to work within this period (0.28, 0.17 to 0.46).” The term “reduced” followed by the hazard ratio greater than 1 was hard for me to understand initially. I appreciate that due to the violation of the proportional hazard assumption this analysis was necessary, but I think you should more clearly describe that the invention decreased the interval until full RTW.

After reading your full description of your skepticism concern the findings for the after 85 days group, I would consider removing this from the abstract.

4. Related to this, the extensive discussion about the limitations of the cox regression model with an important time-varying covariate does present concerns about the basic analytic methodology of the study, even when it is explained clearly and in appropriate detail. If you believe that the results after 85 days are indeed a “statistical flaw” should it be reported more carefully or perhaps placed in an appendix. Many casual readers may never read to the discussion to find the serious concerns about this secondary finding.

This is a well done study with an important finding, and any revisions should be aims at clarifying the findings for readers and insuring the analysis plan has validity and lucidity.

REVIEWER	Gregg Nelson University of Calgary, CANADA
REVIEW RETURNED	11-Jun-2017

GENERAL COMMENTS	<p>This is an interesting study and I applaud the authors efforts for performing such a rigorous trial design. I think there is the potential for this study to contribute to the growing evidence base focused on optimization of the post discharge period. However, I have a couple of questions that I would like the authors to address in their discussion:</p> <ol style="list-style-type: none"> 1. The median time until RTW was 49 days in the intervention group. Given that approx 75% of surgeries were performed by minimally invasive surgery, the RTW time seems excessively long and I wonder about how clinically meaningful the effect of the intervention is. Traditionally, patients who undergo open surgery for benign gynecology surgery are informed that full recovery is 4-6 wks and those who undergo MIS are told that the full recovery is approx half (2-3 wks) or less. 2. A patient's ability to RTW is often very subjective and is influenced by many factors (psychological, interpretation of symptoms and how they impact ability to RTW etc). How was this accounted for in your study? 3. While I agree that patients should be involved in designing their RTW plan, in some cases they may overstate how much time is needed (for obvious reasons). Does the intervention allow the physician to co-manage/change the convalescence plan if it is deemed to be too long (if not this may explain the longer than typical RTW time seen in this study).
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REVIEWER	Jordi Sabadell Department of Obstetrics and Gynecology. Hospital Universitari Vall d'Hebron, Barcelona, Spain.
REVIEW RETURNED	11-Jun-2017

GENERAL COMMENTS	<p>Thank you very much for receiving the opportunity to review the manuscript by Bouwsma et al.</p> <p>The authors present a study with an interesting methodology. A stepped wedge randomised trial is an appropriate design for the objective of the study: to evaluate the effectiveness of an intervention (an Internet-based perioperative care program) at a community level. The authors provide accurately the rationale for the use of this design. Power and sample size justification and calculation are also provided. Statistical methods are given in detail and are appropriate for the study's design. Assumptions for the application of these statistical tests were checked and the authors adapted the analysis accordingly.</p> <p>Finally, the authors have written their manuscript following the CONSORT 2010 cluster extension to cluster randomised trials. For that reasons I have no corrections to suggest regarding the statistical methods.</p> <p>One minor comment arises after reading the article: It is understood from the text that all the centres started the intervention as scheduled, however I would suggest to specify that or, on the contrary, state whether any centre made the crossover to the intervention program later than planned .</p>
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VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1

We thank Reviewer 1 for his compliments on the design and execution of our study. We are pleased he has no concerns regarding the statistical methods.

Response to Reviewer 2

We thank Reviewer 2 for his compliments on the design and execution of our study and we appreciate his remark about the relevance of our work to a general audience and his suggestions to clarify the findings.

Reviewer 2, comment 1: The title does not clearly describe the goal of intervention—to decrease time to full, sustained work activity. Instead of an Internet-based perioperative care programme to enhance postoperative recovery”, I might suggest “a personalized, internet-based programme for expedient return to full work activities” or something that clearly describes the ultimate goal.

Response: We have considered changing the title, however, we believe that the goal of the intervention is enhancing recovery, of which decreased time to full sustainable work can be seen as an objective outcome to operationalize recovery. We therefore would like to maintain the title as it is.

Reviewer 2, comment 2: In the main outcome measures, “Indicators at the level of the patient, the healthcare provider and the organisation were used to measure the degree of implementation of the programme” sentence should be modified to clearly show that this involved an audit of internet-based actions by patients and providers.

Response: We have changed the sentence into: “The degree of implementation of the programme was evaluated at the level of the patient, healthcare provider and organisation by indicators measuring Internet-based actions by patients and providers.”

Reviewer 2, comment 3: In the abstract, I found this important sentence confusing: “Duration to RTW was effectively reduced in the first 85 days after surgery (hazard ratio 2.66, 95% CI 1.88 to 3.77), but the effect was reversed in the small group of patients that did not return to work within this period (0.28, 0.17 to 0.46).” The term “reduced” followed by the hazard ratio greater than 1 was hard for me to understand initially. I appreciate that due to the violation of the proportional hazard assumption this analysis was necessary, but I think you should more clearly describe that the invention decreased the interval until full RTW. After reading your full description of your skepticism concern the findings for the after 85 days group, I would consider removing this from the abstract.

Response: We changed the first part of the sentence, now clearly describing the outcome of faster RTW and avoiding the word “reduced”, which hopefully minimizes the confusion about the second part of this section. We appreciate the reviewers suggestion to remove the findings for the-after-85-days-group from the abstract, however, we believe that we have an obligation to report this as a main result of our primary research question as well, as we want to avoid any pretence of selective reporting by only reporting outcomes in favour of our intervention.

Reviewer 2, comment 4: Related to this, the extensive discussion about the limitations of the cox regression model with an important time-varying covariate does present concerns about the basic analytic methodology of the study, even when it is explained clearly and in appropriate detail. If you

believe that the results after 85 days are indeed a “statistical flaw” should it be reported more carefully or perhaps placed in an appendix. Many casual readers may never read to the discussion to find the serious concerns about this secondary finding.

Response: We reckon the limitations of the cox regression model in our study, however, we strongly believe that our analysis plan has validity and lucidity. At forehand, the non-proportionality of hazards could not have been predicted. As mentioned before, we feel we have an obligation to report the findings after 85 days to avoid publication bias, and therefore, decided not to place this finding in an appendix.

Response to Reviewer 3

We thank Reviewer 3 for acknowledging the potential of our study to optimize perioperative care.

Reviewer 3, comment 1: The median time until RTW was 49 days in the intervention group. Given that approx 75% of surgeries were performed by minimally invasive surgery, the RTW time seems excessively long and I wonder about how clinically meaningful the effect of the intervention is. Traditionally, patients who undergo open surgery for benign gynecology surgery are informed that full recovery is 4-6 wks and those who undergo MIS are told that the full recovery is approx half (2-3 wks) or less.

Response: In the literature there is considerable evidence that the length of recovery time after (gynaecological) surgery systematically exceeds the period considered as appropriate by specialists (see for more details and literature references the protocol of the current study published in JMIR1). The instructions stated above by reviewer 3 are comparable to the convalescence recommendations regarding full sustainable RTW patients received in the intervention group in our study which were: 2 weeks after laparoscopic adnexal surgery, 4 weeks after a vaginal or laparoscopic hysterectomy and 6 weeks after an abdominal hysterectomy). Notwithstanding, time to full RTW was still 49 days which emphasizes the fact that care providers underestimate the length of recovery of their patients, as well as the fact that there is even more improvement to gain in the future. We therefore are very confident that the found effect of our intervention is indeed very clinically meaningful.

In order to clarify this matter, we have added the recommendations regarding full RTW in the paragraph describing the intervention on page 6. Also, we elaborated on this subject in the discussion under the subheading ‘Policy implications and recommendations’ on page 14.

Reviewer 3, comment 2: A patient's ability to RTW is often very subjective and is influenced by many factors (psychological, interpretation of symptoms and how they impact ability to RTW etc). How was this accounted for in your study?

Response: Intention to RTW despite physical complaints as well as expectations towards own recovery were collected at baseline. In the intervention group, patients with a low intention to RTW or inadequate expectations (longer than 3 weeks for adnexal surgery, longer than 6 weeks for vaginal or laparoscopic hysterectomy, or longer than 8 weeks for abdominal hysterectomy) were offered a preoperative consultation with one of the 8 care managers (clinical occupational physicians) to explore the underlying reasons and find ways to optimize these patient factors.

This information can be found in Table 1 and the Online supplementary table S2, as well as in the earlier published protocol, describing the intervention care program in more detail. If Reviewer 3 insists, we can add this information to the main text of the current manuscript as well.

Reviewer 3, comment 3: While I agree that patients should be involved in designing their RTW plan, in some cases they may overstate how much time is needed (for obvious reasons). Does the intervention allow the physician to co-manage/change the convalescence plan if it is deemed to be too long (if not this may explain the longer than typical RTW time seen in this study).

Response: Patients in the intervention group were encouraged to generate a convalescence plan at the web portal, which could be personalized by selecting specific activities that were being relevant to them. These convalescence recommendations were developed through a Delphi method using an expert panel consisting of gynaecologists, general physicians and occupational physicians and are (therefor) in line with current typical beliefs on the resumption of activities following surgery in the Netherlands.² It is important to note that patients were not able to change the length of the recommended recovery times themselves. We specified this in the paragraph describing the intervention on page 6.

The intervention did not restrict physicians to counsel their patients about the postoperative period as they seemed fit. However, we do not expect that there were any physicians who instructed their patients to resume their activities faster than the convalescence advice generated at the web portal. On the contrary, in case of severe (post)operative complications, gynaecologist could choose not to (electronically) approve the generated convalescence plan of their patient and give them specific individual instructions.

As stated before, in our opinion, the relative long duration until RTW found in this study is a good representation of recovery times in general (in the Netherlands), and not a result from conservative convalescence recommendations given to our patients.

Response to Reviewer 4

We thank reviewer 4 for his thorough revision of our manuscript and his approval for the statistical methods used.

Reviewer 4, comment 1: It is understood from the text that all the centres started the intervention as scheduled, however I would suggest to specify that or, on the contrary, state whether any centre made the crossover to the intervention program later than planned .

Response: The following sentence has been added to the results on page 8: “The crossover to the intervention of the 8th cluster was delayed with two months as the number of inclusions in the control group lagged behind compared to the number of inclusions in the intervention group at that time.”.

References used in this response letter

1. Bouwsma EVA, Anema JR, Vonk Noordegraaf A, Knol DL, Bosmans JE, Schraffordt Koops SE, et al. The cost effectiveness of a tailored, web-based care program to enhance postoperative recovery in gynecologic patients in comparison with usual care: protocol of a stepped wedge cluster randomized controlled trial. *JMIR Res Protoc.* 2014;3(2):e30.
2. Vonk Noordegraaf A, Huirne JAF, Brolmann HAM, Van Mechelen W, Anema JR. Multidisciplinary convalescence recommendations after gynaecological surgery: a modified Delphi method among experts. *BJOG.* 2011;118(13):1557-67.

VERSION 2 – REVIEW

REVIEWER	John A. Harris University of Pittsburgh USA
REVIEW RETURNED	27-Jul-2017
GENERAL COMMENTS	Helpful improvements that improve the reading and comprehension in this revision.

	<p>I remain somewhat confused about the publication of some results that the authors themselves describe as may of having "statistical flaws" (see Interpretation of the findings).</p> <p>There are many limitations to the statistical methods any study may use but whenever the authors are convinces of statistical flaws, it seems like this specific analysis should generally not be published. I assume this analysis plan was already planned, and I appreciate the avoidance of excessive or undescribed ad-hoc analysis.</p> <p>One simple option would be changing "statistical flaws" to "statistical limitations". I don't think you are saying there is a flaw as much as you're saying the interpretation of this statistical test may be limited due to its inherent inadequacies.</p>
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REVIEWER	Gregg Nelson Tom Baker Cancer Centre Calgary, Canada
REVIEW RETURNED	21-Jul-2017

GENERAL COMMENTS	The authors have satisfactorily addressed my comments in the initial review.
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REVIEWER	Jordi Sabadell Department of Obstetrcis and Gynecologya. Hospital Universitari Vall d'Hebron. Barcelona. Spain.
REVIEW RETURNED	06-Sep-2017

GENERAL COMMENTS	<p>Thank you for the opportunity to review the revised manuscript by Bouwsma et al.</p> <p>The authors have adequately responded to the prior reviewers' comments/suggestions.</p> <p>I would like to add a minor comment. Owing to the study's design the external validity of the program is obviously limited to populations with internet access. In addition, due to the study's cohort characteristics this perioperative care program seems to be more appropriate for women with at least an intermediate education level. I think that adding a comment on this on the limitations/weaknesses section would be appropriate.</p>
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VERSION 2 – AUTHOR RESPONSE

Response to Reviewer 2

Comment: Helpful improvements that improve the reading and comprehension in this revision.

I remain somewhat confused about the publication of some results that the authors themselves describe as may of having "statistical flaws" (see Interpretation of the findings).

There are many limitations to the statistical methods any study may use but whenever the authors are convinces of statistical flaws, it seems like this specific analysis should generally not be published. I assume this analysis plan was already planned, and I appreciate the avoidance of excessive or undescribed ad-hoc analysis.

One simple option would be changing "statistical flaws" to "statistical limitations". I don't think you are saying there is a flaw as much as you're saying the interpretation of this statistical test may be limited due to its inherent inadequacies.

Response: We thank the reviewer for his suggestion to change the term "statistical flaw" with the term "statistical limitation". We have changed the manuscript accordingly.

Response to Reviewer 4

Comment: Thank you for the opportunity to review the revised manuscript by Bouwsma et al.

The authors have adequately responded to the prior reviewers' comments/suggestions.

I would like to add a minor comment. Owing to the study's design the external validity of the program is obviously limited to populations with internet access. In addition, due to the study's cohort characteristics this perioperative care program seems to be more appropriate for women with at least an intermediate education level. I think that adding a comment on this on the limitations/weaknesses section would be appropriate.

Response: We have added the following paragraph under the section 'Strengths and weaknesses of the study':

As this study only included employed women who had access to Internet and of which the majority was highly educated, caution is needed when generalising the findings. Possibly, clinical effectiveness is reduced when the intervention is accessible to the general audience.

VERSION 3 – REVIEW

REVIEWER	John Harris University of Pittsburgh USA
REVIEW RETURNED	06-Oct-2017

GENERAL COMMENTS	I appreciate the improved wording and explanation of the interpretation of the statistical testing in the discussion.
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REVIEWER	Jordi Sabadell Department of Gynecology. Hospital Universitari Vall d'Hebron. Universitat Autònoma de Barcelona. Barcelona. Spain.
REVIEW RETURNED	29-Sep-2017

GENERAL COMMENTS	Thank you for submitting these revisions, and adequately responding to the prior comments/suggestions. The responses and revisions are satisfactory.
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