Author’s response to reviews

Title: Cost-minimization analysis in a blind randomized trial on small-incision versus laparoscopic cholecystectomy from a societal perspective. Sick leave outweighs efforts in hospital savings.

Authors:

Frederik Keus (erickeus@hotmail.com)
Trudy de Jonge (t.d.jong@elisabeth.nl)
Hein G Gooszen (h.gooszen@umcutrecht.nl)
Erik Buskens (e.buskens@umcutrecht.nl)
Cornelis JHM van Laarhoven (k.vanlaarhoven@chir.umcn.nl)

Version: 2 Date: 6 July 2009

Author’s response to reviews: see over
Thank you for considering our manuscript for publication in Trials.

We thank the reviewers for their useful comments and suggestions. We believe that our manuscript has improved considerably thanks to these comments and suggestions. In our letter below we respond point to point to the comments raised by the reviewers.

On behalf of my coauthors,

Regards,

Frederik Keus
Reviewer's report
Title: Cost-minimization analysis in a blind randomized trial on small-incision versus laparoscopic cholecystectomy from a societal perspective. Sick leave outweighs efforts in hospital savings.
Version: 1 Date: 20 April 2009
Reviewer: Anthony Delaney

Reviewer's report:
Title: Cost-minimization analysis in a blind randomized trial on small-incision versus laparoscopic cholecystectomy from a societal perspective. Sick leave outweighs efforts in hospital savings.
Journal: Trials
Type of article: Research

Thank you for the opportunity to review this manuscript. The authors present the results of a randomised controlled trial to compare the costs of laparoscopic cholecystectomy compared to small-incision cholecystectomy for patients with symptomatic gall-stones and reasonably good health.

1. Is the question posed by the authors new and well defined?
   - The question is not well defined in the manuscript, and could be explicitly stated at the end of the introduction.

   Reply 1
   *We have now explicitly stated the research question at the end of the introduction.*
   *Thank you.*

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
   - The methods for performing the RCT are reasonably well described. The methods for performing the cost minimisation component of the study are reasonably well described.

   Reply 2
   *Thank you.*

3. Are the data sound and well controlled?
   - There is one issue with regards to the data that is of concern. There appears to have been a differential calculation of costs in the two groups. The costs of the laparoscopic equipment is costed separately from the standard operating theatre costs, while for the small incision cholecystectomy the costs of the relevant instruments are not calculated separately. Both sets of instruments require cleaning and sterilisation, both have capitol costs for acquisition and thus for depreciation. Given that the conclusion that small incision is the preferred method is based upon these data, it is important that costs are ascertained in both groups in an identical fashion. The authors should justify why they have identified the additional costs in the laparoscopic group and not the small incision group.
Reply 3
Thank you for pointing to this obscurity. Costs associated with cleaning and sterilization of standard instruments, including capital costs for acquisition and thus for depreciation, have been included in the standard operating theatre costs. This also includes the reusable laparoscopic equipment. The costs for laparoscopic equipment are extra costs associated with the additional laparoscopic equipment (like clips and endobags needed for removal of the gallbladder) other than standard instruments needed to perform the laparoscopic procedure. These equipment and thus the costs are absent in the small-incision procedure. The small-incision procedure does not require extra equipment other than the standard instruments. We have now made this more clear in our methods section.

- There is data missing from Table 4. The direct costs related to complications appear to be a lot greater in the small incision group compared to the laparoscopic group, although a per patient value is not given and p-value is not given for this comparison. The fact that the complication related costs are higher is in the small incision group, and subsequently the overall direct costs are higher in the small incision group, makes the conclusion that the small incision group preferable somewhat harder to believe. The justification given for this in the discussion would be more convincing if it had been specified a-priori.

Reply 4
The data missing from table 4 is missing for a reason. We agree with the peer reviewer that the justification for this should be given a priori.
An average complication cost per patient is difficult to perceive since the large majority of patients have no complications at all. Therefore, average complication costs per patient would not be meaningful. However, another argument even more important is the fact that the trial was not powered to detect a difference in complication costs, since this would require many more patients. Reporting a p-value of a difference in average complication costs between both groups may result in spurious findings and would therefore not be justified. We have now explained this more clearly and moved this section from the discussion section to the methods section so that it is now specified a priori.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
- The reporting of the study could be enhanced by reference to the following paper outlining a guideline for reporting of economic analyses

Reply 5
Thank you for this useful advice. We have now referred to this important paper in our manuscript. We have revised our manuscript using the checklist in this paper and we believe that all relevant items have now been reported in our manuscript.
5. Are the discussion and conclusions well balanced and adequately supported by the data?
- The conclusion that small incision cholecystectomy is the preferred method for performing cholecystectomy in reasonably well patients with symptomatic gall stones is not supported by the evidence found in the study. The total direct costs are greater in the small incision group, and the only advantage for small incision cholecystectomy appears to be in a post hoc analysis performed with the most costly patients excluded. I think a more balanced conclusion is indicated given the all the data available.

Reply 6
We do agree with the reviewer that the intention-to-treat analysis shows that total costs are higher using the small-incision cholecystectomy when all patients including all complications are included. However, when looking at the details of our data we find the true answer to the question which is opposite to the conclusion derived from the intention-to treat analysis. The difference in costs between both surgical techniques is completely reversed when excluding one patient with a complicated recovery. One may look at this as a sensitivity analysis omitting one outlier showing that the intention-to treat data is not robust.

The design of our study (which is reflected in the sample size calculation) was to evaluate differences in costs between both techniques of cholecystectomy. The aim of our study was not to evaluate a difference in costs caused by (random) variations in complications. We know from meta-analyses including over 2500 patients that probably there are no differences in complications at all. Even trial sequential analysis shows that there are no differences considering complications between both techniques (another paper provisionally accepted by the Journal of Clinical Epidemiology). In our study, the random high costs from one patient in the small-incision group could therefore as well have happened in the laparoscopic group.

We do believe that reporting the complication related costs is important to illustrate their potential impact on total costs of cholecystectomy patients. However, for estimating the difference in direct costs apart from random variations in complications we rather could have performed a marginal analysis of direct costs excluding all complication related costs. This much easier analysis would have demonstrated the answer to our question straightforward, but would not have provided an incremental value. However, we prefer to include the perspective that complications substantially add to the total costs. Therefore, we included these costs in our data.

These contrasting findings show the impact that the extreme skewness of cost data may have on the conclusions of our study. We do realize that the random variation causing this skewness does obscure the debate considerably. We have now elaborated these considerations in our discussion.

6. Do the title and abstract accurately convey what has been found?
- The title could probably do without the second sentence. The abstract could be more balanced as noted above.

Reply 7
The reviewer is fully correct that the focus of the trial is on the difference in costs between laparoscopic and small-incision cholecystectomy. However, the results learn us that savings can be achieved much more efficiently when focusing on sick leave. Since this is an important lesson to learn we are reluctant to delete the second sentence of the title. If the editors insist, however, we could delete this second sentence from the title.

We have softened the conclusions in our abstract.

7. Is the writing acceptable?
- The style could be tightened a little in accordance with the guidelines referred to above.

Reply 8
We have now improved our manuscript according to your suggestions.

Major compulsory revisions
- The question is not well defined in the manuscript, and could be explicitly stated at the end of the introduction.
- The authors should justify why they have identified the additional costs in the laparoscopic group and not the small incision group.
- The conclusions should be more balanced. I don’t think there is sufficient evidence presented to warrant the conclusion that small incision cholecystectomy is definitively cheaper than laparoscopic cholecystectomy.
- The finding that there are significant costs associated with loss of employment is interesting, but was not the focus of the study. References to this should be taken out of the title and not given such importance in the abstract, and in the conclusion.
- The authors should explicitly state that results from this study have been previously published twice.
  The paper in Archives of surgery is referred to in the introduction, and the quality of life paper is referred to only obliquely in the methods section.

Reply 9
We have responded to these comments by a point-to-point reply in the previous pages of this letter.

- The authors should provide justification for the use of costs for the sample size calculation. This is an unusual way of looking at sample size, which would more commonly be calculated looking for a clinically meaningful difference in a patient oriented outcome.

Reply 10
The reviewer is correct that it is unusual to focus on costs in a sample size calculation. However, when patient-relevant outcomes appear to be not clinically and statistically different, it seems justified to focus on costs.
In the past, previous trials have evaluated differences in patient-relevant outcomes between laparoscopic and small-incision cholecystectomy. In meta-analyses no differences in patient-relevant outcomes appear to be present between these two techniques. Even multiple meta-analytical methods and trial sequential analyses (paper provisionally accepted by The Journal of Clinical Epidemiology) show that there are no differences between both techniques in patient relevant outcomes. In absence of clear clinical benefit it may therefore be interesting to focus on costs (a secondary outcome measure) associated with the available techniques. A randomized evaluation was chosen in order to reduce bias. Consequently, the sample size calculation for this randomized trial focused on costs to answer this secondary outcome research question.

We hope that we have provided satisfactorily justification for our unusual way of looking at sample size. We have made this clearer in our methods section.

Minor essential revisions
- Some of the language in the manuscript is inappropriate. Examples include:
  - References to laparoscopic cholecystectomy conquering the world
  - The statement that no differences were found in clinical outcome measures between small incision cholecystectomy and laparoscopic cholecystectomy should specify that this was based on the results of a meta-analysis performed by the authors. In fact this section might be better placed in the introduction, to make the argument that a cost-minimisation study needed to be performed.

Reply 11
We have now revised our manuscript accordingly.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests.
Ad
Reviewer's report

Title: Cost-minimization analysis in a blind randomized trial on small-incision versus laparoscopic cholecystectomy from a societal perspective. Sick leave outweighs efforts in hospital savings.

Version: 1 Date: 7 May 2009
Reviewer: Vincent B Nieuwenhuijs

Reviewer's report:

This study focuses on the economic aspects of small incision cholecystectomy (SIC) vs. laparoscopic cholecystectomy. The clinical outcomes of this well-designed RCT have been published recently. Since there were no major differences in clinical outcomes between the 2 techniques the authors postulate that costs may be an important ground to prefer one method above the other. This paper describes the cost analysis of the previously published RCT.

major comments:
Length of hospital stay is an important variable determining hospital costs. On p. 6 it is mentioned that patients left the hospital as soon as they were able to do so. Was the decision to leave the hospital completely left to the patient? If so how was the patient instructed to chose the time of discharge. It is well known that pre-operative information and expectations are a major factor for patients to accept that discharge is safe. Did all patients receive standard information about the procedures and was this information the same for both SIC and LC? What was the role of the doctor on the ward and the nurse in the decision to discharge a patient? Where there any standard discharge criteria? How did they encourage the patient to be discharged? And were they blinded for the operating technique?

Reply 12

The reviewer is fully correct that length of hospital stay is an important variable in determining hospital costs. However, in our meta-analyses we did not find any significant differences in hospital stay between laparoscopic and small-incision cholecystectomy. Findings in our trial that there are no differences in costs associated with hospital stay are in line with the findings from the meta-analyses. The reviewer is also fully correct that pre-operative information and expectations are a major factor for patients to accept that discharge is safe. All patients in our trial received identical (written) pre-operative information. Both the patients and the doctor on the ward and the nurses were blinded to the procedures performed. Only the operating team was aware of the used operating technique. Patients were encouraged to leave the hospital as soon as they felt they were able to do so, but we did not have standard discharge criteria. As all personnel on the ward were blinded as well as the patients, we have no arguments to believe that there were confounding factors influencing hospital stay. Moreover, the findings of our trial are in line with the meta-analyses.

Table 1. Why were preoperative costs recorded and included in the analysis?
Have the authors done an analysis on the post-randomisation costs. Would their conclusions be any different?

Reply 13
In cost-analyses it is essential to include all costs. Differences in costs should be seen in the perspective of all costs associated with the procedure, rather than performing only marginal analyses which would obscure results and discussions. Pre-operative costs are the same in both groups, and performing an analysis excluding these costs would only increase the incremental differences. So, conclusions would not be any different.

Small incision cholecystectomy is a difficult procedure to learn. Due to minimal exposure to the assisting surgeon it may a difficult procedure to supervise. What was the presumed learning curve? Did all residents and surgeons go through the learning curve? Was there any difference in resident experience between the groups. If the LCs were done by less experienced residents this would lead to longer operating time and thus higher costs.

Reply 14
We do not agree with the reviewer that the small-incision cholecystectomy is a difficult procedure to learn. It would be interesting to learn on which experience the pre-assumption of the reviewer is based.
The experience of residents was not recorded, but randomization took place when the patient was in the operating room. So, beforehand the operating team was unaware about which procedure to perform. In a previous paper we reported that we did not find differences in the operating teams (Arch Surg. 2008 Apr;143(4):371-7). Laparoscopic cholecystectomy was the procedure of choice before the start of the trial and all surgeons were experienced in laparoscopic cholecystectomy. Small-incision cholecystectomy was introduced after a pre-trial introductory phase and all surgeons went through a technical learning curve. With a longer introductory phase, differences might have been even more favorable regarding the small-incision technique.

What was the effect of the shorter operative time to estimated costs, since SIC was significantly faster (11.5 min). If this would be the main reason for SIC to be the more economic procedure (operation theatre related costs), than the conclusion would be that the fastest cholecystectomy is the cheapest. This may not be true since 11 min OR time may not lead to less costs for society. Please comment.

Reply 15
The reviewer is certainly correct that operative time contributes significantly to the cost difference. From the second part of table 4 it is clear that the difference in direct costs is caused by the difference in operation theatre related costs. This operation theatre costs are caused by the time difference in procedures and by the costs associated with the extra laparoscopic equipment. Our meta-analyses (of trials with low risk of bias) shows a significant weighted mean difference of 16 minutes in favor of the small-incision technique.
Since time in the operating theatre is expensive and scarce the planning may certainly benefit. When a laparoscopic cholecystectomy takes on average 75 minutes to perform, the difference is the planning of 5 small-incision cholecystectomies
instead of 4 laparoscopic procedures. In the long run this may certainly provide some relief for waiting list problems.

Discussion: when no differences in primary outcomes are found several secondary outcome measures such as costs may be important to prefer one technique over the other. In the paper reporting the clinical outcomes cosmesis was not reported. Which method was preferred on cosmetic grounds by the patient? A couple of well disguised small incisions (LC) may give a better cosmetic result than a single 8 cm incision.

Reply 16
The reviewer is correct that cosmesis was not reported in our paper reporting the clinical outcomes. In our randomized trial we have measured cosmetic results by a validated questionnaire. These results have been reported elsewhere (Surg Endosc. 2008 Jul;22(7):1649-59). We found no differences in cosmetic results between both minimal-invasive techniques. We have now made this more clear in our methods section and included this reference in our manuscript.

Table 4: Unfortunately an outlier in the SIC group skewed the data in this group. Please describe the details of this case. Please also describe the outlier in the LC group. The authors justify the exclusion of the outliers by stating that the data may be distorted. Complications may dependent of the operating technique. It should be made clear that the complications for the outlying case were not procedure related. If the complication is related to the small incision technique it is questionable whether the intention to treat analysis may be aborted. Especially since the conclusion of the study is completely reversed from LC to SIC as being the cheaper method.

Reply 17
The reviewer is fully correct that if complications are dependent of the operating technique, then these complications associated costs should certainly be included in the analysis. However, both outliers were patients with common bile duct injuries with intensive care stay. Intensive care stay is extremely expensive and the patient in the small-incision group had a longer intensive care stay. Our meta-analysis shows no differences in complications between both techniques. We therefore believe that the outlying case in this trial should be considered a random variation. The conclusion of our manuscript should answer the question of cost differences between both techniques rather than concluding on a difference in costs as a consequence of random variations in complications. Excluding all complication related costs leads to an overestimated incremental difference in costs. Therefore, complication related costs were included. However, the outliers caused by random variation heavily influenced the differences in costs and were therefore ignored. Therefore, we believe that the true conclusion to our question that costs of SIC are lower is correct. We have now made these considerations much clearer in our manuscript.
Table 5: employed patients. Probably the outliers were not employed. In this subgroup the difference in total cost is not significant. In the discussion on p.14 the authors hypothesize (based on 21000 cholecystectomies annually in the Netherlands) that a possible reduction of sick leave may result in 8.6 million euro. Both return to work and costs were not significantly different in this subgroup. It is inappropriate to state that SIC may lead to lower costs based on return to work and procedure related costs on non-significant differences. This unfounded assumption should be omitted from the paper.

Reply 18
The reviewer is correct that this issue is not very clearly outlined in our discussion. However, the calculations are not based on differences between LC and SIC. The first part of the last paragraph discusses potential savings irrespective of the used operating technique. The last sentence compares three different options for reaching hypothetical savings, including two options irrespective of the operating technique (reduced hospital stay and quicker return to work). The last option calculates savings based on lower direct costs caused by a change in policy from LC to SIC. We have now made this much clearer in our discussion. We have also stresses more clearly that these calculations are hypothetical.

The authors are very firm in their recommendation that SIC is the procedure of choice based on costs. This is however only supported after exclusion of an outlier thereby neglecting the intention to treat principle. This affects the credibility of the trial. The conclusions in the title, abstract, discussion and conclusion should be less firm in favor of SIC. In the literature the data is also conflicting. I don’t feel this trial will once and for all prove that SIC is less expensive.

Reply 19
The reviewer is correct that we are very firm in our recommendation that SIC is the procedure of choice. In our reply 17 we have argued why we think it is justified to omit one outlier from the analysis and why it is that the intention-to-treat analysis provides incorrect conclusions. Therefore we believe our conclusion that SIC is less costly remains justified. We would also like to refer to our reply 6 to the comment of the other reviewer. However, we have softened our conclusions in the title, abstract, discussion and conclusion.

Has SIC replaced LC as the method of choice for a cholecystectomy in the hospitals of the authors? If so, please add that to the discussion of the manuscript. This would confirm that the authors are willing to change their local policy according their strong recommendation in their manuscript. If not, why not?

Reply 20
Both techniques LC and SIC are being applied in our hospital with an increasing use of SIC. Awaiting final results of the various chapters derived from the RCT, as well as from the meta-analyses published (Cochrane Library 2006, issue 4, Art.No.: CD004788,
CD006231, and CD006229) and to be published (Overview of systematic reviews, expected in Cochrane Library 2009, issue 4) the change from LC to SIC may increase further not only in our hospital but also in other hospitals closely following the results of these studies.

Minor comment
In the methods section registrars are mentioned whereas in the discussion they are called residents, please use one term.

Reply 21
We have made corrections. Thank you.

**Level of interest:** An article of importance in its field  
**Quality of written English:** Acceptable  
**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.
Reviewer's report

Title: Cost-minimization analysis in a blind randomized trial on small-incision versus laparoscopic cholecystectomy from a societal perspective. Sick leave outweighs efforts in hospital savings.

Version: 1 Date: 8 May 2009
Reviewer: klaas hendrik H in't hof

Reviewer's report:
Interesting article. The article would be stronger if the authors extend the calculations and explanation about the costs on a society level.

Reply 22
Thank you for your comment. We have provided sensitivity calculations in the last paragraph of the discussion extending our findings to a national level including a societal perspective.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.