PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

<table>
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<th>TITLE (PROVISIONAL)</th>
<th>Health economic evaluation of the Lund Integrated Medicines Management Model (LIMM) in elderly patients admitted to hospital</th>
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<td>AUTHORS</td>
<td>Ghatnekar, Ola; Bondesson, Åsa; Persson, Ulf; Eriksson, Tommy</td>
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VERSION 1 - REVIEW

<table>
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<th>REVIEWER</th>
<th>Joakim Ramsberg, Chief scientific officer Swedish Agency for Health and Care Services Analysis Sweden</th>
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<td>REVIEW RETURNED</td>
<td>09-Jul-2012</td>
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THE STUDY

The references to the literature where the utility weights are found is missing. At least I can't find it.

GENERAL COMMENTS

A well written and interesting paper!

I found a couple of typos (e.g. p34L20: ..4 times..) so I would suggest that the authors go over the text just once more.

P5, methods. I suggest showing the decision tree in a figure. It helps the reader.

P5.L38: why only 3 months? Are there no effects and costs after 3 months? You need to explain that to the reader.

P5, methods: state and explain your chosen perspective of analysis.

P6. Admission part. The study intervention included both an admission and a discharge part. Is this a problem when conclusions are drawn only about the admission part?

P6, L11: Why include "possible" re-admissions? It is not in line with data in the discharge part on the same page, L39. Even better would have been to analyse ALL hospitalisations to avoid this discussion completely.

P7, disutilities: I can't find the reference to the literature where the utility weights are from?

P8: Explain why you chose to calculate utility like this? The utility loss is very substantial indeed, but only lasts for a day: why not longer? What about patients who experience a drug related problem but doesn't seek health care?

P15, L30: Did intervention patients on average have much higher hospitalisation costs in the study? This could be due to chance but not necessarily. Cost data is typically much too skewed and
truncated at zero (a few patients have very large costs, while most have none) for anything but very large studies to pick up a significant difference. Your study was probably only powered to detect a difference in efficacy and it is therefore interesting to consider if there could there be some other reason behind the difference than chance. I agree that it will not alter the conclusions. This can also be discussed on p17, L 29.

P17, L15 and on: Why is the potential greater for review at admission?

P18, L39: I would still argue that 6 months is better in order to capture all costs and effects and I think it is up to the authors to convince the reader why 3 months is better. Likewise, I think basing the analysis on all hospitalisation costs is better as it avoids a potential bias in assigning causality (a subjective process). Randomisation takes care of differences in patient characteristics and co-morbidities between study arms, so that argument is not valid.

REVIEWER

Susanna Wallerstedt, MD, Ass Prof
Department of Clinical Pharmacology
Sahlgrenska University Hospital
Göteborg, Sweden

I have no competing interests.

REVIEW RETURNED

13-Jul-2012

THE STUDY

The quality of a health economics evaluation is dependent on the quality of the underlying studies. This manuscript is based on clinical studies with historical controls (Midlov et al, Pharm WOrl Sci 2008;30:840-845, Hellstrom et al, Eur J Clin Pharmacol 2011;67:741-52), whereas a randomized controlled design would have been preferable. Indeed, in a recent systematic review (Arch Intern Med, published online June 25, 2012), the quality of both underlying studies in this manuscript has been assessed as poor (grading: poor – fair – good). In my opinion, an economic evaluation of clinical studies with poor quality adds little valuable information, and it cannot be out ruled that the results are biased, with an increased chance of gaining results in favour of the intervention (as reported).

The figures used in the health economics model, as tabulated in Table 1, are derived from the two poor quality studies and are not credible from a scientific evidence perspective; the systematic review on hospital-based medication reconciliation practices, mentioned above, revealed inconsistent results concerning post-discharge healthcare utilization (improvement in only 2 out of 8 studies).

Clinical pharmacist interventions have been shown to reduce medication errors, but the clinical relevance remains unclear. Indeed, a protocol has been provided in 2011 on a Cochrane systematic review on medication reviews of hospitalized patients to prevent morbidity and mortality, emphasizing the apparent need of a comprehensive analysis, and the review is soon to be published. As a matter of fact, clinical pharmacist interventions often focus on
“potential harms”. Such “potential harms” are not appropriate to include in a health economics evaluation. Thus, it may be preferable to omit “Probability of prescription error” (included in Table 1 in page 6, first paragraph) from the model.

Furthermore, I wonder about the correctness of separating the LIMM model in two parts, when doing the health economics evaluation, that is, the admission and the discharge part. Maybe it is preferable to analyze the intervention as a whole.

The estimations of time consumption in the control and the intervention group seem unrealistic. For example, no physician time was included in the intervention group, although medication errors found by pharmacists need to be fed back to physicians for assessments if prescribing changes are needed. Both time for feedback and time for potential ordering changes should be included (pharmacists do not have the right to prescribe in Sweden). To illustrate the magnitude of the time consumption, it was shown in a Swedish report that the additional physician time needed for a computerized prescribing support system (the physicians did not handle the system themselves, they only received alerts after overflow alerts had been removed by another personnel category, and made appropriate prescribing changes where necessary) was 15-30 minutes per day for a senior physician, and 15-30 minutes per patient (90-180 minutes per day) for a junior physician (the latter perform most of the practical work in Sweden). Furthermore, much of the time spent by physicians and nurses in the control arm should probably be spent anyway, that is, also in the intervention arm, since ordering drugs need to be performed in all patients, as must a discharge discussion with the patient.

REPORTING & ETHICS

Conflicts of interest statements need to be provided. For example, it need to be made clear that Apoteket Farmaci AB, the employer of the last author, provides medication reviews for sale (pharmacist consultations), and may thus have an economic interest in the results. It also needs to be clarified that IHE, the affiliation of the first and the third author, provides health economics evaluations upon request, and financial arrangements for the present study should be disclosed.
months. However, we thought that extrapolating costs and effects arbitrarily to e.g. 6 months or 12 months might introduce unnecessary uncertainty to the analyses. Therefore we chose the 3-month perspective. We have tried to clarify this in the text.

P5, methods: state and explain your chosen perspective of analysis.
Comment: Clarified by “Indirect costs for production losses were not considered as the analysed cohort was assumed to be retired.”

P6. Admission part. The study intervention included both an admission and a discharge part. Is this a problem when conclusions are drawn only about the admission part.
Comments: Both the admission and discharge part include medication reconciliation. To avoid misunderstanding we have revised the conclusion.
P6, L11: Why include "possible" re-admissions? It is not in line with data in the discharge part on the same page, L39. Even better would have been to analyse ALL hospitalisations to avoid this discussions completely.
Comment: In the studies included in this manuscript drug related re-admissions were the main outcome measure and the studies were not powered to demonstrate effects on total re-admissions. In both studies the probability that the admission was drug related was evaluated by blinded experts using the WHO criteria for causality (certain, probable, possible, no) were used. (World Health Organisation–Uppsala Monitoring Centre. The use of the WHO-UMC system for standardised case causality assessment. Available at: http://www.who-umc.org/graphics/4409.pdf). We agree that there might be misunderstanding and have corrected the text

P7, disutilities: I can't find the reference to the literature where the utility weights are from? Comment: Our mistake. This is now corrected.

P8: Explain why you chose to calculate utility like this? The utility loss is very substantial indeed, but only lasts for a day: why not longer?
Comment: since we didn't know for what reason the patients attended outpatient care we assumed a "one-off" disutility. This was to encompass both length and/or severity of the condition. We have changed the wording to better explain this.

What about patients who experience a drug related problem but doesn't seek health care?
Comment: we didn’t have information on patients experiencing problems but not seeking care.
P15, L30: Did intervention patients on average have much higher hospitalisation costs in the study? This could be due to chance but not necessarily. Cost data is typically much too skewed and truncated at zero (a few patients have very large costs, while most have none) for anything but very large studies to pick up a significant difference. Your study was probably only powered to detect a difference in efficacy and it is therefore interesting to consider if there could there be some other reason behind the difference than chance. I agree that it will not alter the conclusions. This can also be discussed on p17, L 29.
Comment: from the data used it was not possible to discern if there existed any bias in the hospitalisation. Therefore we performed several sensitivity analyses to analyse the importance of this difference in hospitalisation costs. We have elaborated on this further below in the discussion.

P17, L15 and on: Why is the potential greater for review at admission?
Comment. On p12L15 we clarified that it is the probability of re-hospitalisations that constitute the main cost off-set.
P18, L39: I would still argue that 6 months is better in order to capture all costs and effects and I think it is up to the authors to convince the reader why 3 months is better. Likewise, I think basing the analysis on all hospitalisation costs is better as it avoids a potential bias in assigning causality (a subjective process). Randomisation takes care of differences in patient characteristics and co-morbidities between study arms, so that argument is not valid.
Comment: as explained above we do not have information on re-hospitalisations and out-patient visits beyond month 3. In order to avoid introducing more uncertainty we prefer a 3-month analysis.

Reviewer: Susanna Wallerstedt, MD, Ass Prof
Department of Clinical Pharmacology
Sahlgrenska Universitet Hospital
Göteborg, Sweden

I have no competing interests.

The quality of a health economics evaluation is dependent on the quality of the underlying studies. This manuscript is based on clinical studies with historical controls (Midlov et al, Pharm Worl Scı 2008;30:840-845, Hellstrom et al, Eur J Clin Pharmacol 2011;67:741-52), whereas a randomized controlled design would have been preferable. Indeed, in a recent systematic review (Arch Intern Med, published online June 25, 2012), the quality of both underlying studies in this manuscript has been assessed as poor (grading: poor – fair – good). In my opinion, an economic evaluation of clinical studies with poor quality adds little valuable information, and it cannot be out ruled that the results are biased, with an increased chance of gaining results in favour of the intervention (as reported).

The figures used in the health economics model, as tabulated in Table 1, are derived from the two poor quality studies and are not credible from a scientific evidence perspective; the systematic review on hospital-based medication reconciliation practices, mentioned above, revealed inconsistent results concerning post-discharge healthcare utilization (improvement in only 2 out of 8 studies).

Clinical pharmacist interventions have been shown to reduce medication errors, but the clinical relevance remains unclear. Indeed, a protocol has been provided in 2011 on a Cochrane systematic review on medication reviews of hospitalized patients to prevent morbidity and mortality, emphasizing the apparent need of a comprehensive analysis, and the review is soon to be published. As a matter of fact, clinical pharmacist interventions often focus on “potential harms”. Such “potential harms” are not appropriate to include in a health economics evaluation. Thus, it may be preferable to omit “Probability of prescription error” (included in Table 1 in page 6, first paragraph) from the model.

Comment: the probability of prescription error is necessary for the probabilistic sensitivity analysis in order to estimate the number of prescription errors identified at discharge. This probability was based on Midlov et al., Clinical outcomes from the use of Medication Report when elderly patients are discharged from hospital, Pharm World Scı 2008;30:840–845

Furthermore, I wonder about the correctness of separating the LIMM model in two parts, when doing the health economics evaluation, that is, the admission and the discharge part. Maybe it is preferable to analyze the intervention as a whole.

Comment: In fact the analysis is performed as an entity. The division in two parts is for improving understanding of the results as to where the gains accrue – in the admission or discharge part.

The estimations of time consumption in the control and the intervention group seem unrealistic. For example, no physician time was included in the intervention group, although medication errors found by pharmacists need to be fed back to physicians for assessments if prescribing changes are needed. Both time for feedback and time for potential ordering changes should be included (pharmacists do not have the right to prescribe in Sweden). To illustrate the magnitude of the time consumption, it was shown in a Swedish report that the additional physician time needed for a computerized prescribing support system (the physicians did not handle the system themselves, they only received alerts after overflow alerts had been removed by another personnel category, and made appropriate prescribing changes where necessary) was 15-30 minutes per day for a senior physician, and 15-30 minutes per
patient (90-180 minutes per day) for a junior physician (the latter perform most of the practical work in Sweden). Furthermore, much of the time spent by physicians and nurses in the control arm should probably be spent anyway, that is, also in the intervention arm, since ordering drugs need to be performed in all patients, as must a discharge discussion with the patient.

Comment: The estimation of time consumption is derived from publication 29 (http://ejhp.bmj.com/content/early/2012/03/30/ejhpharm-2012-000096.abstract). This time utilization and questionnaire based study indicates that LIMM-based pharmacist activities take 1 h per patient and result in major time savings for physicians and nurses (of at least 2 h per patient) in all the areas (hospital, primary and community care). Detailed information can be found in the publication.

Conflicts of interest statements need to be provided. For example, it need to be made clear that Apoteket Farmaci AB, the employer of the last author, provides medication reviews for sale (pharmacist consultations), and may thus have an economic interest in the results. It also needs to be clarified that IHE, the affiliation of the first and the third author, provides health economics evaluations upon request, and financial arrangements for the present study should be disclosed.

Comment: All conflict of interests will be provided to BMJ Open.

VERSION 2 – REVIEW

REVIEWER
Susanna Wallerstedt, MD, Ass Prof
Department of Clinical Pharmacology
Sahlgrenska University Hospital
Göteborg, Sweden

REVIEW RETURNED
05-Sep-2012

THE STUDY
I do not consider the authors’ responses to my comments and questions adequate. They have chosen to comment on a few, and to leave out the most important ones. Their responses indicate ignorance within the field, and, according to my assessment, the paper is not scientifically sound, leaving out important limitations and drawing firm conclusions from poor data. In fact, the main problem with the present study is that the underlying data are poor, and a health economics evaluation on poor data will be misleading. Furthermore, their choice of wordings suggests that the purpose of the paper is to promote their intervention, rather than to objectively make a scientific evaluation.

REPORTING & ETHICS
I scrutinized the provided conflicts of interest, and noticed that these may not have been properly described by the last author. It need to be made clear that he is an employee of Apoteket Farmaci AB, the company which has probably paid for this health economics evaluation (to the Institute of Health Economics, where the first and third authors are employed). It also has to be made clear that Apoteket Farmaci AB is a private company which sells pharmacist services to the healthcare (pharmacists are only very rarely involved in patient care in Sweden).

GENERAL COMMENTS
The authors have not responded adequately to my comments and questions. They have not at all commented upon the fact that their health economics evaluation is based upon studies of poor scientific quality, and what problems this may implicate. Indeed, the conclusions are much too firm, and a proper discussion on these limitations is missing. In addition, I believe that the conflicts of interest forms are incompletely filled in. According to my understanding, the last author is an employee of a company which may have paid for this health economics evaluation (see the conflicts of interest statements of author one and three). This private company also sells pharmacist services to the healthcare. Indeed, these conflicts of interest need to be made clear to the reader.
Furthermore, I agree with the other reviewer that an analysis on all hospitalization costs would have been preferable; assessments on causality can introduce bias, especially if the study design is of low quality and the assessors are not perfectly blinded (which is not probable within a study with historical controls where medical records are to be scrutinized). In addition, I still do not understand why prescription errors need to be included in the model. All you should need is the incremental cost of the intervention and the incremental benefits in monetary terms (e.g. reduced hospitalizations). When it comes to costs of the intervention, I was surprised by the response by the authors. A pharmacist is not permitted to prescribe in Sweden. Thus, their efforts need to be forwarded to the prescribing doctor to be executed. It thus seems unrealistic that the additional time spent on an intervention patient for a doctor could be zero. The costs for the intervention should also include time for pharmacist – doctor communication, and doctor prescribing. The authors refer to a publication in a journal without impact factor, with which I am not acquainted. I could not access the full paper and could thus not assess the quality and if the study was scientifically sound.

VERSION 2 – AUTHOR RESPONSE

With regard to the rebuttal it was felt that the study does look potentially publishable, however, with: more transparent reporting of the primary study's design - as now described below in your rebuttal. It wasn't ideal, as it wasn't an RCT. But it was probably stronger than the reviewer felt (she said "especially if the study design is of low quality and the assessors are not perfectly blinded, which is not probable within a study with historical controls where medical records are to be scrutinized" and that now seems wrong: it was a controlled pre-post study and the outcomes were assessed blind. The revised paper could and should explain all that and then discuss the remaining limitations of that design, i.e. that you could not rule out all bias and confounding because it wasn't an RCT.

We have inserted the systematic review article as a reference and commented on the level of quality in our study and the limitations from our study in the discussion. We have also commented on potential bias from team-based interventions. If this statements are not appropriate based on the argument with the reviewer it can be deleted.

Furthermore, I agree with the other reviewer that an analysis on all hospitalization costs would have been preferable; assessments on causality can introduce bias, especially if the study design is of low quality and the assessors are not perfectly blinded (which is not probable within a study with historical controls where medical records are to be scrutinized).

Since we do not have access to data on all hospitalisations we have accommodated the reviewer's comment by adding the following sentence in the Discussion section (p.17): "Still, historical controls’ medical records were scrutinised to identify “certain”, “probable” or “possible” hospital readmissions, which may introduce bias from either too strict or too loose rules for causality."

In addition, I still do not understand why prescription errors need to be included in the model. All you should need is the incremental cost of the intervention and the incremental benefits in monetary terms (e.g. reduced hospitalizations).

Perhaps we misunderstood the reviewer's comment in the first round. We thought she was interpreting the word “probability” as “potential” when it in fact is a way of denoting a risk-variable. This is the standard denomination in health economics.

The reason why we include prescription errors at all is that although the number of errors is reduced with the LIMM-model, they are not completely eradicated. As a prescription error needs to be handled by a physician we include this time (cost) in the model. The model is not limited to hospitalisation costs. Hence, as the reviewer correctly remarks, we account for the incremental benefits (prob
prescription error control - prob prescription error intervention) for reduced physician time spent on correcting prescription errors in monetary terms. I hope this clarified it.

“A pharmacist is not permitted to prescribe in Sweden. Thus, their efforts need to be forwarded to the prescribing doctor to be executed. It thus seems unrealistic that the additional time spent on an intervention patient for a doctor could be zero. The costs for the intervention should also include time for pharmacist – doctor communication, and doctor prescribing.”

We have not studied the exact time for each activity. The total time spent on LIMM and non-LIMM based services have been evaluated by a questionnaire (ref 27, 28). There is a total net saving on time spent and the physicians cost for prescribing as well as the communication is already included in the model (table 1, Drug review cost per patient), but not disaggregated by staff. In short, time for pharmacist – doctor communication and doctor prescribing are included. We agree that this has not been clearly communicated in the text. We have added the following sentence in Methods/Unit costs and dis-utilities: “Intervention costs include both pharmacist’s and physician’s time for review, communication, prescription, training and quality checks.”

Full disclosure of the competing interests as now explained in your rebuttal:
Tommy Eriksson was at the time of the study research pharmacist at the Hospital Pharmacy, Lund University Hospital, and head of research and development at Apoteket Farmaci AB. Apoteket Farmaci AB is part of Apoteket AB, a state owned company which was the owner of all Swedish pharmacies including hospital pharmacies, and had a government contract to promote better use of medicines. The LIMM-project started 13 years ago as part of this contract, and these studies were conducted before the mission ended, July 2009. The project was conducted in cooperation with Lund University Hospital and Lund University. Apoteket Farmaci AB has possibly commercial interest in disseminating the LIMM-model.
Apoteket Farmaci AB did not fund this health economic evaluation. The authors from IHE were paid by Dr Eriksson’s research account, money which derived mainly from compensation for presentations based on the LIMM-model, other educational- and research activities, channelled through Apoteket Farmaci AB.