PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Pharmacist provided medicines reconciliation within 24 hours of admission and on discharge: A randomised controlled pilot study</th>
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<tbody>
<tr>
<td>AUTHORS</td>
<td>Cadman, Brit; Wright, David; Bale, Amanda; Barton, Garry; Desborough, James; Hammad, Eman; Holland, Richard; Howe, Helen; Nunney, Ian; Irvine, Lisa</td>
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VERSION 1 - REVIEW

| REVIEWER           | Nina Barnett
<table>
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<tr>
<td></td>
<td>Medicines Use and Safety Division, NHS specialist pharmacy service, England, United Kingdom.</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>31-Aug-2016</td>
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GENERAL COMMENTS

Thank you for this interesting paper which is an important addition to research in the area. I welcome the inclusion of the MRC complex intervention guidance for this topic. This paper highlights to readers that counting interventions from medicines reconciliation is not enough (alone) to justify the resource implications and I welcome the pragmatic approach taken to piloting in this study and the robustness both of MRP support, data collection and patient follow up. It is interesting to note that while a significant minority of control patients received MR during their stay, most discrepancies were not followed up.

Given the UK one month readmission cost implication for trusts, I agree that an RCT using one month data may be desirable as well as 3 months. I suggest that if readmissions are to be measured in response to the MR process, readmission data should focus on unplanned medicines related readmissions at 3 months to identify which could have been avoided through appropriate Medicines reconciliation. This may require peer review of 3 month readmissions to assess reasons for readmission unless the trust codes for medicines related readmission are not required. Please reference figure 1 (sources of SOP created)

Amendments: Please confirm ethics approval or reasons not required.

REVIEWER

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Stephen Byrne</th>
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<tr>
<td></td>
<td>School of Pharmacy, University College Cork, Cork, Ireland</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>07-Sep-2016</td>
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GENERAL COMMENTS

Thank you for asking me to review this interesting paper. My comments below, I feel would strengthen this publication.

Title:
Consider including the term “pharmacist provided” as this is more reflective of what was done. Secondly should the term discharged
be included in the Title?

Abstract:
Consider clearly defining in the abstract who performed the intervention.
Does usual care include a Med Rec, if so what proportion of people and who performs this, pharmacists or pharmacy technicians? What proportion of the control group underwent a MR, how was this controlled for??

With regards to secondary outcomes: a follow up study of 1120 patients would be beneficial to demonstrate a 6% reduction of emergency Hospital readmission rates, would it be better to look in the future at all readmission and not just emergency readmission, would this figure be higher? This is at odds with the main outcome proposed for the follow up study, of re-hospitalisations within 3 months?

Page 7:
the nurse in charge advised that the patient was not suitable to be approached (even though NPSA and NICE recommend it be done for all patients. Medicines reconciliation may be done without interacting with the patient. further explanation is required.

Page 8 the mean total time was 48.6 minutes which is very time consuming relative to the control, further comment on this and the potential impact on the cost effectiveness is warranted.

GP records available for 53% of the unintentional discrepancies in the control group seems, low, please clarify.

Page 9,
LOS rates are skewed due to a small number staying for a prolonged period of time, what would the rate be if these outliers were removed?

With regards to the control group 62 people still had unresolved med rec issues. This asks a question regarding the validity of the med rec process in the control arm. Why were these discrepancies not resolved, please clarify?

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Alemayehu Berhane Mekonnen</th>
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<tr>
<td>University of Sydney, Sydney, Australia</td>
<td>10-Sep-2016</td>
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<table>
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<th>GENERAL COMMENTS</th>
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<td>It is an interesting pilot study covering a wide ranging of outcomes, and hopefully the future trial would generate a robust evidence of the impact of pharmacist provided medication reconciliation on important clinical outcomes, including hospital re-admissions. Whilst taking length of stay as a primary outcome measure to assess the impact is suitable as the authors mentioned, however, it is not a strong measure for interventions such as medication reconciliation where effects are observed long after the intervention is done. In that aspect, I shared the findings from the pilot study, and authors can also reconsider other crude outcomes (e.g. mortality, composite outcomes). Although the manuscript is well written and articulated, yet it needs major changes before publication. For ease of review, I have organized my comments in to sections.</td>
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Title
Medication reconciliation was also conducted for discharge, and seems need modification for the title.

Abstract
Why 6% reduction was considered for your sample size calculation for your future trial as far as your pilot study result showed a reduction rate of 8.6%.

Background
Page 4, lines 13-17. It needs some change in rewording.
Page 4, lines 19-22. I couldn’t catch up what is the needed message of this sentence.
Page 4, line 37. Change ‘upon’ to up on.

Method
- Try to edit your figure; there is a shift in arrows as it currently appears.
- Have you done post-discharge follow-up?
- It is not clear how many pharmacists were involved in MR activities. To strengthen the statement mentioned in lines 20-21, there should be a clear statement regarding this, including the type(s) of pharmacists (e.g. research pharmacist/hospital pharmacist).
- Up to where MRPs followed identified unintentional medication discrepancies whether they had been resolved or not.

Control
- Thought it was described that the SOP followed in the intervention was not followed in the control arm, it is not clear yet what the MR components involved in the control group. It is not enough to delimit MRPs to the intervention arm only. Also, there should be a clear distinction between the MR activities employed in both groups. The other important thing to reconsider, for your future RCT, is to include MR components that would yield an enhanced intervention.

Intervention fidelity
- You can delete ‘five’ here as far as you revise as of the recommendation above.

Inclusion criteria
- Not clear patients with how many number of medications were included.
- Whereas your intention is to evaluate a MR service within 24 hrs of admission, I can noticed that you have also included a patient for whom MR was undertaken after 24 hrs of admission. It is not line with your inclusion criteria.
- Any other exclusion criteria…?
- You tried to figure out what the control group is receiving (lines 11-15). But what my concern is patients under this group can have a possibility of receiving MR service post-randomisation. Don’t you think this would affect the outcomes at discharge and subsequent outcomes evaluated post-discharge, as far as you had employed the same groups of patients from patient admission to discharge. This should be explicitly detailed on top of the analysis.

Outcome measures
If you intend to evaluate a mix of process and crude outcomes, it is essential to start with assessing the process outcomes (i.e. unintentional discrepancies) although your main motive is to measure another suitable outcome; that is, LOS. You might probably rewrite this part at this point or reconsider in your future RCT.

Unintentional discrepancy identification
- Are trained nurses involved in MR services? Try to differentiate what MRPs and trained nurses were doing?
- During clarification of the identified discrepancies, whom you had contacted? Or you simply categorise with the information available
only. If so, please briefly put as this might overestimate the incidence of unintentional discrepancies. Also, I cannot see anywhere the definition of unintentional medication discrepancies.

Results
Page 7, line 54. Back space before the number ‘198’.
Page 7, line 58. Change ‘data was’ to ‘data were’.
Page 8, lines 3-7. I am not clear why you are interested to measure and report the time taken by the pharmacy team to deliver MR in both the intervention and control arms. If you have a plan to translate this into cost data, that would be fine. Otherwise, it is confusing if we are in the position of comparing both arms in terms of that.
Page 8, lines 10-11. Reword this statement.
Page 8, lines 19-21. As it currently written, it is difficult what the numbers refer to.
Page 8, line 25. ‘Data were’ not ‘was’.
Page 8, lines 44-46. As I commented it above, it is not clear from where the 6% reduction is obtained.

REVIEWER
Torsten Hoppe-Tichy
University Hospital of Heidelberg
Pharmacy Department
Germany

REVIEW RETURNED 13-Oct-2016

GENERAL COMMENTS
I think that one should point out that it is not only about MedRec on admission but also on discharge. Perhaps the outcome is significantly influenced by the MedRec at discharge. That should be discussed. I have the feeling that the discharge process has a greater influence on the outcome than the process within 24 hours of hospital admission.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Thank you for this interesting paper which is an important addition to research in the area. I welcome the inclusion of the MRC complex intervention guidance for this topic. This paper highlights to readers that counting interventions from medicines reconciliation is not enough (alone) to justify the resource implications and I welcome the pragmatic approach taken to piloting in this study and the robustness both of MRP support, data collection and patient follow up. It is interesting to note that while a significant minority of control patients received MR during their stay, most discrepancies were not followed up.

Given the UK one month readmission cost implication for trusts, I agree that an RCT using one month data may be desirable as well as 3 months. I suggest that if readmissions are to be measured in response to the MR process, readmission data should focus on unplanned medicines related readmissions at 3 months to identify which could have been avoided through appropriate Medicines reconciliation. This may require peer review of 3 month readmissions to assess reasons for readmission unless the trust codes for medicines related readmission

Thank you for the positive comments

Amendments: Please confirm ethics approval or reasons not required.
This is provided at the end of the paper as per requirements from journal (page 11)

Please reference figure 1 (sources of SOP created)

The SOP was based on that used within the hospital trust. Have included statement to that effect in the paper. (Page 5)

Reviewer: 2

Thank you for asking me to review this interesting paper. My comments below, I feel would strengthen this publication.

Title:
Consider including the term “pharmacist provided” as this is more reflective of what was done.

Have changed accordingly

Secondly should the term discharged be included in the Title?

Have added this in to improve clarity

Abstract:
Consider clearly defining in the abstract who performed the intervention.

Pharmacist included in introduction

Does usual care include a Med Rec, if so what proportion of people and who performs this, pharmacists or pharmacy technicians?

This information is provided in the results of the paper – proportions now included (30.4% by pharmacist and 30.4% by pharmacy technician)

What proportion of the control group underwent a MR, how was this controlled for??

Following inserted into the abstract and repeated in the main results:
95(99%) of patients in the intervention received MR within 24 hours, whilst 62(60.8%) of control patients received MR

The analysis was conducted from an ‘intention to treat’ perspective. Consequently, comparisons were made on the basis of the arm they were allocated to, regardless of the care actually received. This data is provided in the main text. (page 8)

With regards to secondary outcomes: a follow up study of 1120 patients would be beneficial to demonstrate a 6% reduction of emergency Hospital readmission rates, would it be better to look in the future at all readmission and not just emergency readmission, would this figure be higher?

We have assumed that routine/planned admissions would be the same in each arm and the intervention is designed to prevent unplanned readmissions.

This is at odds with the main outcome proposed for the follow up study, of re-hospitalisations within 3 months?
The term unplanned has been included in the main text for clarity (Page 8). The abstract already states emergency readmission.

Page 7:
the nurse in charge advised that the patient was not suitable to be approached (even though NPSA and NICE recommend it be done for all patients. Medicines reconciliation may be done without interacting with the patient. further explanation is required.

The nurse identified those who could not be approached for consent to participate in the study. This was not consent to receive the service. All patients not approached received usual care.

Clarity regarding this is provided in the text (Bottom page 5)

‘The nurse in charge of the ward confirmed that it was appropriate for the patient to be approached to be consented to participate in the study’

Page 8 the mean total time was 48.6 minutes which is very time consuming relative to the control, further comment on this.

Following text included in the discussion (Middle page 9):

‘The study SOP required pharmacists to undertake initial MR, follow up on all interventions to ensure that discrepancies had been addressed, assess all discharge letters for accuracy and correct them. Patients in the control arm frequently did not always receive all four elements and this probably explains most of the difference in time provided.’

and the potential impact on the cost effectiveness is warranted

We consider that the following points in the Discussion address this issue (Page 10)

“This study was a pilot study and was not designed to obtain a definitive answer to whether MR provided to all patients within 24 hours of admission was cost-effective.”

“…there is an additional cost associated with providing the intervention and therefore high quality evidence from a multi-centre RCT is now needed to determine both its effectiveness and cost-effectiveness.”

GP records available for 53% of the unintentional discrepancies in the control group seems, low, please clarify.

We have no insight into the possible causes for this but recognise that requires addressing in a future study in the discussion (page 10):

‘Not all primary care medication lists were made available to researchers and approaches to addressing this will require consideration for a future definitive study.’

Page 9,
LOS rates are skewed due to a small number staying for a prolonged period of time, what would the rate be if these outliers were removed?

The geometric mean provides this value in Table 2
With regards to the control group 62 people still had unresolved med rec issues. This asks a question regarding the validity of the med rec process in the control arm. Why were these discrepancies not resolved, please clarify?

We acknowledge that this questions the quality of the MR process in the control arm and the following sentence is already provided in the discussion in recognition of this: (Page 9)

‘The majority of discrepancies identified in the control arm by the researchers were however found not to have been resolved and therefore reasons for the relative ineffectiveness of the control arm MR requires elucidation through a detailed process evaluation.’

The inclusion of the following paragraph in response to an earlier comment should provide some insight for the reader (page 9):

‘The study SOP required pharmacists to undertake initial MR, follow up on all interventions to ensure that discrepancies had been addressed, assess all discharge letters for accuracy and correct them. Patients in the control arm frequently did not always receive all four elements and this probably explains most of the difference in time provided.’

Reviewer: 3

Please leave your comments for the authors below

It is an interesting pilot study covering a wide ranging of outcomes, and hopefully the future trial would generate a robust evidence of the impact of pharmacist provided medication reconciliation on important clinical outcomes, including hospital re-admissions. Whilst taking length of stay as a primary outcome measure to assess the impact is suitable as the authors mentioned, however, it is not a strong measure for interventions such as medication reconciliation where effects are observed long after the intervention is done. In that aspect, I shared the findings from the pilot study, and authors can also reconsider other crude outcomes (e.g. mortality, composite outcomes). Although the manuscript is well written and articulated, yet it needs major changes before publication. For ease of review, I have organized my comments in to sections.

Thanks for the comments

Title
Medication reconciliation was also conducted for discharge, and seems need modification for the title.

This has been amended

Abstract
Why 6 % reduction was considered for your sample size calculation for your future trial as far as your pilot study result showed a reduction rate of 8.6%.

This is a conservative estimate based on one standard error below actual difference seen. Text amended accordingly in main results (Page 8).

Background
Page 4, lines 13-17. It needs some change in rewording.

Removed the second ‘and that’ and summarised the sentence
Page 4, lines 19-22. I couldn’t catch up what is the needed message of this sentence.

Sentence amended as follows (Page 4):

‘Data on cost-effectiveness which usually underpins recommendations made by NICE (12) is not available and therefore whether this intervention represents an appropriate use of NHS resources is unknown’

Page 4, line 37. Change ‘upon’ to up on.

Changed to ‘on’

Method

Intervention
- Try to edit your figure; there is a shift in arrows as it currently appears.
Done

Have you done post-discharge follow-up?

We report data provided from GP surgeries which was used to identify the proportion of discrepancies which translated through to primary care. We also were able to follow up most patients at 3 months and these data are reported.

It is not clear how many pharmacists were involved in MR activities. To strengthen the statement mentioned in lines 20-21, there should be a clear statement regarding this, including the type(s) of pharmacists (e.g. research pharmacist/hospital pharmacist).

5 different hospital pharmacists provided the intervention. Text amended accordingly (page 5).

Up to where MRPs followed identified unintentional medication discrepancies whether they had been resolved or not.

Prior to discharge. Text amended accordingly (Page 5).

Control

Thought it was described that the SOP followed in the intervention was not followed in the control arm, it is not clear yet what the MR components involved in the control group. It is not enough to delimit MRPs to the intervention arm only. Also, there should be a clear distinction between the MR activities employed in both groups. The other important thing to reconsider, for your future RCT, is to include MR components that would yield an enhanced intervention.

This is a pragmatic trial where it was not possible to not provide MR in the control arm or ethical to provide different elements to different groups when the hospital has a policy of all patients requiring MR within 24 hours of admission. The study shows that routine MR performed within the hospital seemed to have little impact on discrepancies and this difference between ideal service provided through research and real service provided in practice is discussed.

The insertion of the following paragraph in response to the earlier reviewer should help the reader to
understand the difference (page 9).

‘The study SOP required pharmacists to undertake initial MR, follow up on all interventions to ensure that discrepancies had been addressed, assess all discharge letters for accuracy and correct them. Patients in the control arm frequently did not always receive all four elements and this probably explains most of the difference in time provided.’

Intervention fidelity

- You can delete ‘five’ here as far as you revise as of the recommendation above.

Deleted

Inclusion criteria

- Not clear patients with how many number of medications were included.

‘At least one’ added (Page 5)

- Whereas your intention is to evaluate a MR service within 24 hrs of admission, I can noticed that you have also included a patient for whom MR was undertaken after 24 hrs of admission. It is not line with your inclusion criteria.

In response to this comment we have amended Figure 2 (the CONSORT) to clarify that this participant did not receive the intervention as per the protocol.

The participant met the inclusion criteria and was recruited and randomised as per protocol. However they did not receive MR within 24 hours: When the pharmacist went to provide the service they had left the ward and therefore did not receive the service. The following sentence is provided in the results explaining this anomaly (Page 8).

One patient in the intervention arm did not receive the MR as he was not on the ward when the pharmacist visited. Data were erroneously not collected for this patient post randomisation.

- Any other exclusion criteria…?

No

- You tried to figure out what the control group is receiving (lines 11-15). But what my concern is patients under this group can have a possibility of receiving MR service post-randomisation. Don’t you think this would affect the outcomes at discharge and subsequent outcomes evaluated post-discharge, as far as you had employed the same groups of patients from patient admission to discharge. This should be explicitly detailed on top of the analysis.

60.8% of control arm patients received MR post-randomisation. This is explicitly stated in the paper. It did not seem to affect outcomes and this is discussed.

Outcome measures

If you intend to evaluate a mix of process and crude outcomes, it is essential to start with assessing the process outcomes (i.e. unintentional discrepancies) although your main motive is to measure another suitable outcome; that is, LOS. You might probably rewrite this part at this point or reconsider in your future RCT.

The point of this paper is to identify a clinical outcome which is sufficiently sensitive to the intervention and is meaningful to patients. Process measures tend to overinflate the problem as they require the
reader to assume that their occurrence will result in a future clinical outcome. We have shown that many unintentional discrepancies, our primary process measure, don’t actually translate into incorrect drug alterations in the patient records post-discharge.

We fully accept that our initial choice of length of stay was incorrect and build an argument for unplanned admission 3 months post-discharge. We do not believe that this is crude or that a future trial should be powered on process measures. We do accept that process measures are important as they enable the reader to identify the potential causes of the change in clinical outcome measures seen and have reported these throughout the paper.

Table 2 presents the process measures and table 3 the clinical outcomes which is in the order suggested by the reviewer.

Unintentional discrepancy identification
Are trained nurses involved in MR services? Try to differentiate what MRPs and trained nurses were doing?

Nurses were not directly involved in the process. We identified no interventions delivered by them.

During clarification of the identified discrepancies, whom you had contacted? Or you simply categorise with the information available only.

If so, please briefly put as this might overestimate the incidence of unintentional discrepancies.

The following paragraph is provided in the discussion in anticipation of this concern (Page 9).

‘When identifying unintentional discrepancies, we have assumed that both the MRP generated list in the intervention arm and the RA generated list in the control arm were accurate. Both are unrealistic assumptions and ideally within a definitive study all data should have been reviewed independent of the service and blinded to group allocation. The unblinded identification of medication discrepancies and inability to confirm intentional or unintentional nature of errors in many instances also means that the data on unintentional discrepancies must be treated with further caution.’

Also, I cannot see anywhere the definition of unintentional medication discrepancies.

Following inserted in the text (Page 6):
‘defined as differences between patient records with no identifiable rationale’

Results
Page 7, line 54. Back space before the number- ‘198’.

Amended
Page 7, line 58. Change ‘data was’ to ‘data were’

Amended
Page 8, lines 3-7. I am not clear why you are interested to measure and report the time taken by the pharmacy team to deliver MR in both the intervention and control arms. If you have a plan to translate this into cost data, that would be fine. Otherwise, it is confusing if we are in the position of comparing both arms in terms of that.
One of the reasons for the feasibility study is to determine whether costs can be accurately identified, measured and valued. This demonstrates that the service delivery cost can be captured in both arms.

Page 8, lines 10-11. Reword this statement.

Amended

Page 8, lines 19-21. As it currently written, it is difficult what the numbers refer to.

UDs added in for clarity (Paragraph 3)

Page 8, line 25. ‘Data were‘ not ‘was’.

Amended

Page 8, lines 44-46. As I commented it above, it is not clear from where the 6% reduction is obtained.

This is now clarified

Reviewer: 4

I think that one should point out that it is not only about MedRec on admission but also on discharge. Perhaps the outcome is significantly influenced by the MedRec at discharge. That should be discussed. I have the feeling that the discharge process has a greater influence on the outcome than the process within 24 hours of hospital admission.

The title has been amended to highlight the fact that MR was delivered at both ends of the admission

The trial was a feasibility study to determine whether future research via a definitive study is possible. We are unable to comment on the exact causes of the differences seen and relative impact of the different elements of the intervention. We have however amended the discussion to better reflect the fact that the inclusion of the discharge element for all patients may be an important element here (Page 9).

‘With a hospital requirement that all patients receive MR within 24 hours of admission it is unsurprising that two thirds of the control arm received some form of MR during their hospitalisation, a quarter of which received this within 24 hours. There is no specific requirement for MR on discharge however and this may explain some of the differences seen between the two groups. The majority of discrepancies identified in the control arm by the researchers were found not to have been resolved and therefore reasons for the relative ineffectiveness of the control arm MR requires elucidation through a detailed process evaluation.’
Pharmacist provided medicines reconciliation within 24 hours of admission and on discharge: a randomised controlled pilot study

Brit Cadman, David Wright, Amanda Bale, Garry Barton, James Desborough, Eman A Hammad, Richard Holland, Helen Howe, Ian Nunney and Lisa Irvine

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