Pharmacy provided medicines reconciliation within 24 hours of admission: A randomised controlled pilot study

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Pharmacy provided medicines reconciliation within 24 hours of admission: A randomised controlled pilot study

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Background
The UK government currently recommends that all patients receive medicines reconciliation (MR) from a pharmacy within 24 hours of hospital admission. This is currently not undertaken for every patient and the associated cost-effectiveness is unknown. A pilot study to inform the design of a future randomised controlled trial to determine effectiveness and cost-effectiveness was undertaken.

Method
Patients were recruited seven days a week from five adult medical wards in one hospital over a 9 month period and randomised using an automated system to intervention (MR within 24 hours of admission and at patient discharge) or usual care which may include MR (control). Recruitment and retention rates were determined. Length of stay (LOS), quality of life (via EQ-5D-3L), unintentional discrepancies (UDs) and emergency re-admission (ER) within 3 months were all tested as outcome measures. The feasibility of identifying and measuring intervention associated resources was determined.

Result
200 patients were randomised to either intervention or control. Groups were comparable at baseline. The intervention resolved 250 of the 255 UDs identified at admission. Only 2 UDs were identified in the intervention group at discharge compared with 268 in the control. The median LOS was 94 hours in the intervention arm and 118 hours in the control, with ER rates of 17.9% and 26.5%, respectively. Assuming 5% loss to follow up, 1120 patients (560 in each arm) are required to detect a 6% reduction in 3 month ER rates.

Conclusions
The results suggest that changes in outcome measures resulting from MR within 24 hours were in the appropriate direction and readmission within 3 months is the most appropriate primary outcome measure. A future study to determine cost-effectiveness of the intervention is feasible and warranted.

Strengths and limitations
• Pilot randomised controlled trial
• Intervention fidelity enhanced through competency assessment of medicine reconciliation providers
• Robust process for identifying unintentional discrepancies at each stage developed to prevent results contamination
• Pragmatic design and therefore elements of the intervention found within the control arm
• Limited response to request for patient data 3 months post-discharge

Main points
• No robust evidence exists for the cost-effectiveness of medicines reconciliation provided at both admission and discharge to hospital by members of the pharmacy team
• This paper reports a pilot study to determine the design of a future RCT of medicines reconciliation
• The anticipated number of patients were recruited and the data obtained was of sufficient quality to enable translation into a future study
• The control arm, as part of ‘usual care’, received some level of medicines reconciliation however this seemed to have minimal impact on unintentional discrepancies
• Rehospitalisation within 3 months is the most suitable primary outcome measure for a future definitive study
Background
Medicines Reconciliation (MR) is defined by the World Health organisation as ‘the formal process in which healthcare professionals partner with patients to ensure accurate and complete medication information transfer at the interfaces of care’. (1) Researchers have identified unintentional error rates within hospital prescriptions on admission of between 30-70% (2-5) and these can include omission of usual medicines, prescription of incorrect dosages and addition of medicines which have not been previously prescribed. The majority of these errors are believed to result from deficiencies in the MR process with such errors known to contribute to patient morbidity and mortality and increase the length of hospital stay (LOS). (6-10)

Consequently, within the UK, patient safety guidance issued by the National Patient Safety Agency (NPSA) and the National Institute of Health and Care Excellence (NICE) recommended that policies for MR should be implemented in hospitals for all adult patient admissions, and that pharmacy should be involved in the MR process and that this should be within 24 hours of admission. (11) NICE guidance on pharmacy involvement was based primarily on one randomised controlled trial (RCT) which demonstrated that the inclusion of the pharmacist in MR reduced the error rate from 44% to 19%. (2) The threshold of a cost per QALY of between £20000 and £30000 used by NICE when deciding which interventions the NHS should adopt (12) was not used to inform this recommendation as robust data to support this was not available.

Recent systematic reviews of hospital based medicines reconciliation practices consistently demonstrate a reduction in medicine discrepancies, however this has not been shown to result in reductions in post-discharge healthcare utilisation. (13, 14) When considering only pharmacist-led medicines reconciliation interventions a 19% reduction in the rate of all cause readmissions was seen but similarly pooled data on mortality and composite readmission and emergency department visit did not find in favour of either pharmacist-led intervention or usual care. (15)

With the significant resources required for pharmacists to deliver medicines reconciliation services it is not adequate to demonstrate reduction in errors (which may or may not result in adverse drug events), it is also important in resource limited health systems to show that such investment constitutes value for money. There is currently a recognised lack of evidence supporting the cost-effectiveness of medicines reconciliation interventions provided by pharmacists. (16) A model built in 2008 to estimate the likely cost-effectiveness of preventing medication error at hospital admission using medicines reconciliation suggested that a pharmacist based intervention is likely to be cost-effective but was based solely upon USA error data and made assumptions concerning the severity of errors prevented. (17)

Despite national guidance few hospitals are providing MR as envisioned by NICE for all patient admissions. (18) Thus, it would appear that further high quality evidence which demonstrates cost-effectiveness is required to ensure that resources are appropriately allocated to this service in order to meet national recommendations. The most suitable approach to determine the cost-effectiveness of a complex intervention such as medicines reconciliation is to perform a RCT which collates data on cost from the appropriate perspective and outcomes which are most proximal to the intervention. Within the UK it is additionally necessary to collect data on quality of life and mortality to enable the cost per quality adjusted life year to be estimated. Recent guidance however suggests that before an RCT of such nature is undertaken feasibility testing and piloting are required. (19)

Aims
The aim of this study was therefore to pilot a randomised controlled trial to inform the design of a future definitive study to determine the clinical and cost-effectiveness of pharmacy providing a full MR service on admission and at discharge. The objectives of the pilot study were to
• identify the most suitable outcome measure for a future definitive trial with respect to proximity and response to the intervention and quality of data obtained
• determine potential recruitment and retention rates
• develop and test the process for measuring resource utilisation associated with the
intervention and use of other NHS services

Method

Study design and location
The trial was randomised controlled pilot study undertaken at Cambridge University Hospitals
NHS Foundation Trust (CUHFT) on five adult medical wards from a range of medical
specialities where patients did not routinely receive MR from a pharmacist within 24 hours of
admission. One similar ward was identified as a “backup”, in the eventuality that one of the
study wards was closed for any reason (e.g. norovirus outbreak) during the recruitment
period.

Intervention
A standard operating procedure (SOP), outlined in Figure 1, was used to deliver MR by a
trained medicines reconciliation pharmacist (MRP) within 24 hours of admission (including
weekends) and at the point of transfer of care out of hospital, or as soon as possible following
patient discharge from hospital to the next care provider. MRPs covered for each other’s
holidays, sick leave and absences wherever possible.

MRPs recorded all unintentional discrepancies they identified between the information they
collated and the inpatient medication chart on admission and again any differences between
the inpatient chart and discharge letter. MRPs followed up on all identified unintentional
discrepancies to ensure that they were addressed.

Control
Patients in the control arm received usual care which may or may not consist of medicines
reconciliation and where it was provided it may not have occurred within 24 hours and could
either be delivered by a pharmacist or pharmacy technician. The MRPs within the
intervention arm did not deliver MR to control patients and the SOP used for study
intervention purposes was not automatically followed within the control arm. For the purposes
of the study all MR details regarding interventions undertaken within the control arm were
recorded and costed.

Intervention fidelity
To enhance intervention fidelity all five MRPs were observed by the Principal Investigator (PI)
on at least 3 occasions to confirm adherence to the SOP. All MRPs had provided MR to more
than 30 patients in the year previous to delivering the intervention for the trial.

Recruitment
A recruitment target of 200 patients was set for the nine month pilot phase. Study wards were
visited every morning by the research assistant (RA) during the study period to identify
potential participants. The nurse in charge of the ward confirmed that it was appropriate for
the patient to be approached regarding the study. Patients were recruited based on the
following inclusion and exclusion criteria.

Inclusion criteria:
• Adult (≥18 years of age)
• Admitted with prescribed medicines to one of the five medical wards
• Patient had not already received MR from the pharmacy team as part of routine
  pharmaceutical input at the time of recruitment
• Identified from hospital computer system as having been admitted straight from the
  Emergency Department (ED) to one of the five participating wards within the previous 24
  hours

With the intervention required to be delivered within 24 hours of admission, patients were
given a maximum of 2 hours to consider whether they wished to participate. Intervention
patients received MR in accordance with the SOP. Information obtained by the RA for the
purposes of the study was given to the MRP pharmacist prior to the visit to prevent
duplication of effort and to ensure the patient was not interviewed for the same information
twice.

Randomisation was performed utilising the Norwich Clinical Trials Unit automated service with
patients stratified by ward. When wards were later closed for infection control reasons,
participants on the "backup" ward were randomised and stratified as if they had entered the
closed ward.

Patients randomised to the control group received usual care; this may have included
elements of MR by members of the pharmacy team and in some cases may have occurred
within 24 hours of admission but post-randomisation. Whilst this may have affected patients in
the control arm an intention to treat analysis was performed and consequently for the purpose
of the analysis patients they remained in their allocated arm.

Outcome measures
Although undertaken as a pilot study with study aims to identify the most suitable outcome
measure, length of stay (LOS) was nominally selected as the primary outcome measure for
this pilot trial. Secondary outcome measures were unplanned (emergency) re-admission at 3
months, quality of life (EQ-5D-3L) and unintentional discrepancies.

Data collection
To enable comparison of intervention and control groups, age, gender, primary reason for
admission, all co-morbidities and the admission ward was recorded. Additionally consented
patients or their third party consultees completed a quality of life score (EQ-5D-3L) on
admission, including the related visual analogue scale (VAS).

LOS, reported in hours, was calculated as the difference in time from arrival at the hospital to
the time of discharge as recorded in the hospital information system (HISS). Unplanned re-
admissions to the intervention hospital within the 3 months post-discharge were also obtained
from HISS. EQ-5D-3L responses were also obtained via postal survey 3 months post-
discharge, allowing the calculation of Quality Adjusted Life Years (QALYs) (21) in the
subsequent economic evaluation.

Unintentional discrepancy identification
To enable the identification of unintentional discrepancies the following information was
photocopied by the research associate (RA) for all consented patients (both intervention and
control) and stored securely:
- All versions of the inpatient medication chart(s) and discharge letters,
- Medical notes during admission
- GP medication list on admission
- GP medication list at 3 month post discharge (when received from GP surgery)
- Any additional medicines related information brought in by the patient on admission e.g.
copies of labels from patient medicines, handwritten or typed medicine lists.

The RA was a trained nurse and consequently was experienced in medical data collation and
extraction.

3 months post discharge the stored information was used to develop an 'accurate medication
list' for the control arm patients by the research team on admission and at discharge. These
were then compared with the inpatient chart on admission and discharge letter to identify any
discrepancies. Medical notes were subsequently reviewed, unblinded to group allocation, to
enable differentiation between those which were unintentional i.e. discrepancies which could
not be explained from the information available and those which were intentional.

The GP medication list obtained 3 months post discharge (where available) was used to
enable the identification of discrepancies which still remained at 3 months. Without access to
GP medical notes it was not possible to establish whether identified discrepancies were
unintentional.
All potential discrepancies which were identified at the 3 month point as having translated into the patient notes were reported to the patient’s GP.

**Resource use**
The time taken by the pharmacy team to deliver the MR was monitored in both the intervention and control group (if applicable). Additionally, the following items were requested in both groups:

- Time in hospital (Length of stay)
- Medication (in patient medication and GP medication list at 3 months)
- Re-hospitalisations
- Other health care contacts

With the exception of the final item, which included all health professional contacts and was requested from the participant at 3 months post discharge, these were extracted from medical records.

**Sample size calculation**
As a pilot study a formal power calculation was not performed. The consequences for the precision of the primary outcome variable (LOS) of the choice of sample-size were however estimated. Summary statistics on LOS taken from a study undertaken at St James Hospital, Dublin (22) gave quartiles for two groups as (3, 7, 5) and (2, 5, 12) days. To derive an estimate of variability from this, an underlying log-normal distribution was assumed, which is consistent with the position of the medians, and its standard deviation estimated using the geometric mean of the ratios between the upper and lower quartiles. This produced an estimated SD of 1.26 which implied that a comparison between 2 groups of 100 patients, would provide an expected half-width for the 95% confidence interval of the difference between group-means (on the natural log scale) of 0.35. Translated back to the confidence interval for the ratio of average length of stay between the intervention and control groups would extend by a factor of about 1.4 either side of the point estimate.

**Data analysis**
As a pilot study descriptive statistics were utilised to determine the suitability of the different outcome measures and report the variation in the differences in order to determine a sample size for a future randomised controlled trial. Similarly, completion rates are reported for each source of resource use data and the EQ-5D-3L.

The primary outcome variable, length of stay, was reported using median, arithmetic mean and geometric mean. The rate of Trust re-admissions, Trust emergency re-admissions and mortality are also reported for both arms, along with the mean change in the VAS from the EQ-5D-3L.

**Results**
Nine hundred and nineteen patients were assessed for eligibility of which 224 did not meet inclusion criteria. 200 out of 310 patients who were subsequently approached by the RA consented to take part in the study (Figure 2). Of those patients identified as potentially eligible but not approached this was primarily because either the nurse in charge of the ward advised that the patient was not suitable to be approached or that the end of the 24 hour window for intervention was due to expire.

Recruitment took place between July 2012 and April 2013 (9 months and 2 weeks), resulting in a recruitment rate of 5.2 patients per seven days.

There was one post-randomisation exclusion in each arm (they were subsequently found not to meet the inclusion criteria), and were accordingly excluded from all analyses. Table 1 thereby summarises the characteristics of the remaining 198 participants (96 intervention 102 control). The groups were broadly comparable.

One patient in the intervention arm did not receive the MR as he was not on the ward when the pharmacist visited. Data was erroneously not collected for this patient post randomisation.
The time taken by the pharmacist to deliver the intervention was recorded for the remaining 95 intervention participants, where the mean total time was 48.6 minutes (range 2 to 195 minutes). In the control group, 31 participants received input from a pharmacist (mean reported time 15 minutes) and 31 had input from a pharmacy technician (mean reported time 12 minutes), for 25 of these patients this occurred within the 24 hour window.

During the initial hospital admission three participants died, with a further 11 deaths during the three months follow-up period (see Figure 2). In total six intervention patients died and 8 control patients over the trial period (p=0.78, Fisher’s Exact). Additionally, in the control arm, one participant was lost to follow up (address not known) and one participant withdrew. After taking account of the 1 patient who did not receive the MR and a further loss to follow-up in the intervention arm, this left a total of 88 available cases in the intervention arm and 92 available cases in the control arm at final assessment point. In terms of outcomes, there was complete data available on LOS and re-admission data.

Table 2 provides a summary of the unintentional discrepancies which were identified at each stage. 16 (16%) intervention patients had no discrepancies at admission and discharge, compared to 12 (12%) control patients. Overall, 2 were known to remain at discharge in the intervention arm compared with 268 in the control group. Neither of the unintentional discrepancies in the intervention arm identified at discharge were present at 3 months.

One hundred and fifty four unintentional discrepancies identified in the control arm were potentially related to medicines to be prescribed post-discharge i.e. the remainder related to medicines prescribed during admission only. Due to the limited number of GP records provided at 3 months data was only available for 82 (53.2%) unintentional discrepancies in the control arm at 3 months and 37 out of the original 154 (24%) were found from the medical records provided to have been propagated into the patient notes.

Table 3 provides a comparison of patient outcomes for the intervention and control group. The results suggest that LOS, mortality and rehospitalisation rates tend to be lower in the intervention arm although statistical significance was not demonstrated as 95% Confidence Intervals overlapped. Based on those who responded, both groups had a higher mean quality of life (based on the VAS) at the 3 month follow up with improvement higher in the control arm. This difference between groups was not significant.

With regard to the response rates for the resource use data there were complete data available (for those upon whom it was requested) for length of stay, medication data as part of the original admission, re-admissions (to the same hospital) and the intervention pharmacist times. Of the 62 controls for whom pharmacist/pharmacy technician review occurred the times were missing for N=27. At 3 month follow-up, medication data were retrieved from GPs for 86 participants (94.5% of those from whom it was requested) in each arm and 133 participants completed and returned both the EQ-5D-3L and the health resource use questionnaires (66 Intervention, 67 Control) (73.5% of those requested from all living participants).

Based on the pilot data we calculate that for a full trial 1120 patients would need to be recruited to detect a 6% reduction in 3 month re-admission rates from a starting point of 26% with 90% power, using a 5% significance level and assuming 5% loss to follow up.

Discussion

The results from this study which was performed to inform the design of a future randomised controlled trial suggest that even though medicines reconciliation activities are taking place such a trial is feasible with reasonable recruitment and retention rates and that both cost and outcome data can be effectively obtained.

We consider that emergency rehospitalisation within 3 months would be the most appropriate primary outcome measure for such a trial, as unlike the other outcome measures tested, it reflects all of the MR activity which occurs in both secondary and primary care. Furthermore, data collection was complete and this is a patient-orientated outcome, unlike medication errors which whilst representing a patient safety issue are a measure of the prescribing process.
Due to the need to recruit patients before they received MR as usual care this reduced the
generalisability of the sample with all of those who had already received MR being
automatically excluded. This was further compounded by recruitment activities which were
focussed towards mornings.

With a requirement that all patients receive MR within 24 hours of admission it is not
surprising that two thirds of the control arm received some form of MR during their
hospitalisation, a quarter of which received this within 24 hours. 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 further elucidation.

The average time spent on the intervention found within this study was very similar to that
reported in a MR time and motion study(23) but three times greater than that in the control
arm. It has been suggested that organisations are probably unlikely to repeat the benefits
from MR services reported in the literature if there are deficiencies in intervention intensity
and breadth.(24) The results from the control arm of this study support this assertion and
suggest that if MR of a similar nature to that seen in the intervention arm was to be shown to
be cost-effective then this would require significantly more pharmacist time.

The proportion of patients screened for eligibility and eventually recruited to the study was
20% and this could have been improved by increasing the number of weekends covered
(from 80% to 100%). Although some patients were not suitable for inclusion in the study as
they had already been reviewed by a member of the pharmacy team prior to being
approached by the RA, there was a sufficient number of patients available for recruitment.

When identifying unintentional errors we have assumed that the MRP in the intervention arm
had created an accurate list with no errors. This is an unrealistic assumption and ideally
within a definitive study the 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.

The process of collating all medicines related data at different time points and sealing it until 3
months post discharge provides an opportunity to identify discrepancies without adversely
affecting the intervention. Whilst the identification of unintentional discrepancies should be
undertaken blind of allocation the resources required for this may not be warranted when
considering that the intentional or unintentional nature of the discrepancy cannot always be
accurately determined.

Considering evidence published post-study completion, limiting the study population to those
over the age of 70 and including a post-discharge telephone call as part of the intervention
may have further enhanced the intervention.(13)

In line with previous research the intervention prevented a large number of unintentional
medicines related discrepancies both during admission and post-discharge.(3-6) The data
obtained suggests that just less than a quarter of unintentional discrepancies identified at
discharge were found to actually translate into primary care records at three months. Whilst
reasons for non-translation were not elucidated the research suggests that the use of number
of unintentional discrepancies at discharge as an outcome measure may over-emphasise the
problem.

Not all primary care medication lists were made available to researchers and approaches to
addressing this will require consideration for a future definitive study. Utilising data on
‘unplanned readmission at 3 months’ would seem to be the most appropriate primary
outcome measure for a future definitive study as it is a patient orientated outcome which is
most likely to reflect the effect of errors which occur at all stages of the process. Similar to
hospital readmission, LOS is a cost which would be captured in any cost-effectiveness
analysis. LOS was however found to be largely skewed by a small number of individuals who
were admitted for extended periods. Furthermore, it is not affected by errors which translate into primary care i.e. does not reflect the full impact of the service. Within the UK hospitals are penalised for unplanned readmissions within one month of discharge and therefore collection of this data may also be warranted for a UK based definitive study.

Unplanned readmission has been used as a primary outcome measure within other similar MR trials (25-29). Whilst differences in unplanned readmission at three months have been demonstrated,(28, 29) this has frequently not been the case at either one or six months.(25-27) Within the first month patients may still be using the medication they were discharged with and consequently this may lessen the impact of errors on the discharge letter resulting from incorrect translation into primary care. Kwan et al. after systematically reviewing the literature suggest that unplanned readmission data should probably be collected for more than 30 days post-discharge.(14) Unplanned readmission at six months will be affected by more factors unrelated to the index admission than at 3 months and therefore it may be more difficult to identify the impact of MR intervention using this outcome measure.

Quality of data collection with respect to LOS, mortality and readmission rates was high as this information was available from hospital records. Resource utilisation data and quality of life scores were however only available for two thirds of participants at follow up. Consequently researchers powering a definitive study on readmission rate will need to consider the possibility of there being more missing data for the cost-effectiveness analysis and imputation of missing data (30) may be necessary to address this.

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Contributors:
BC, EH, DW, JD, RH participated in the conception and design of this study. AB, BC, DW, GB, IN, LI participated in the analysis of the data and interpretation of the results AB, BC, DW drafted the article and all other authors performed critical review of the article. All authors approved the submission of this article

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Competing interests:
None

Ethical approval:
Ethical approval was received on 14th June 2012 from NRES Committee East of England - Essex Research Ethics Committee. Reference number: 12/44/0143

Provenance and peer review
The trial was registered on 5th August 2012: ISRCTN23949491
The trial received competitive funding from NIHR Research for Patient Funding stream and was peer reviewed as part of this process.
Figure 1  Outline of service standard operating procedure

Admission
- Patient interviewed to confirm allergy status and medicines being taken
- GP letter/fax reviewed to confirm allergy status and medicines prescribed
- Medical notes reviewed to confirm any intentional medication changes due to clinical status of patient
- Other sources of information may have been used depending on availability and relevance to current admission by virtue of the date, and included
  - previous electronic discharge letter
  - clinic letter
  - patient’s own drugs (PODs)
  - patients relative or carer
  - nursing home record
  - medication administration record (MAR)
  - modified dosage system (MDS)
- An accurate medication list was documented in the medical notes by the intervention pharmacist

Discharge
- Discharge letter compared with the final drug chart to ensure correct
- Medical notes reviewed
- Changes to medicines field on the electronic system was completed by the intervention pharmacist to communicate intentional medication changes to the GP
- All medicines were added to the discharge letter to ensure a complete record at the point of transfer of care
Figure 2 Consort diagram

Enrolment

Assessed for eligibility (n=919)

Excluded (n=719)
• Not meeting inclusion criteria (n=224)
• Declined to participate (n=110)
• Other reasons (n=385)

Randomised (n=200)

Excluded post-randomisation (n=1 #95)
Not meeting inclusion

Enrolment

Allocation

Excluded post-randomisation (n=1 #154)
Not meeting inclusion

Intervention arm (n=96)
• Received intervention < 24 hr (n=95)
• Received intervention > 24 hr (n=1) #75

Control arm (n=102)
• < 24 hour by pharmacist (n=13)
• < 24 hour by technician (n=22)
• > 24 hour by pharmacist (n=18)
• > 24 hour by technician (n=9)
• No MR performed (n=40)

Discharge follow up

Lost to follow up (n=0)
Death (n=2) #108 #136

Lost to follow up (n=1) #63
Withdrawn (n=1) #173
Death (n=4) #16, 55, 76, 80, 86, 99, 198

Lost to follow up (n=1) #70
Withdrawn (n=0)
Death (n=4) #51, 68, 82, 97

3 month follow up

Data availability

Complete self-reported cost data (n=66)
EQ5D data available at 3 months (incl. deaths) (n=72)
Medication data received from GPs at 3 months (n=78)
Medication data not provided at 3 months (n=12 plus n=6 RIPs)

Complete self-reported cost data (n=66)
EQ5D data available at 3 months (incl. deaths) (n=75)
Medication data received from GPs at 3 months (n=85)
Medication data not provided at 3 months (n=9 plus n=8 RIPs)
### Table 1  Comparison of demographics at baseline:

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<th>Control (n=102)</th>
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<td>No. (%)</td>
<td>45 (46.9)</td>
<td>60 (58.8)</td>
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<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>67.6 (19.0)</td>
<td>65.4 (20.2)</td>
</tr>
<tr>
<td>Regular medicines</td>
<td>Mean (SD)</td>
<td>5.84 (4.07)</td>
<td>6.67 (4.64)</td>
</tr>
<tr>
<td>As required medicines</td>
<td>Mean (SD)</td>
<td>0.85 (2.08)</td>
<td>0.95 (2.53)</td>
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<td>Ward</td>
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<tr>
<td>1</td>
<td>No. (%)</td>
<td>26 (26.8)</td>
<td>27 (26.2)</td>
</tr>
<tr>
<td>2</td>
<td>No. (%)</td>
<td>30 (30.9)</td>
<td>30 (29.1)</td>
</tr>
<tr>
<td>3</td>
<td>No. (%)</td>
<td>10 (10.3)</td>
<td>9 (8.7)</td>
</tr>
<tr>
<td>4</td>
<td>No. (%)</td>
<td>14 (14.4)</td>
<td>16 (15.5)</td>
</tr>
<tr>
<td>5</td>
<td>No. (%)</td>
<td>16 (16.4)</td>
<td>14 (13.5)</td>
</tr>
<tr>
<td>6</td>
<td>No. (%)</td>
<td>1 (1.03)</td>
<td>7 (6.8)</td>
</tr>
<tr>
<td>EQ5D Quality of life (Visual Analogue Scale)</td>
<td>Mean (SD)</td>
<td>55.9 (23.2)</td>
<td>54.7 (23.5)</td>
</tr>
<tr>
<td>Reason for admission</td>
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<td></td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>No. (%)</td>
<td>9 (9.2)</td>
<td>11 (10.7)</td>
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<tr>
<td>Troponin –ve chest pain</td>
<td>No. (%)</td>
<td>7 (7.2)</td>
<td>4 (3.9)</td>
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<tr>
<td>Heart failure</td>
<td>No. (%)</td>
<td>2 (2.1)</td>
<td>5 (4.9)</td>
</tr>
<tr>
<td>Exacerbation Chronic</td>
<td>No. (%)</td>
<td>4 (4.1)</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Obstructive Pulmonary Disease</td>
<td>Other No. (%)</td>
<td>73 (75)</td>
<td>79 (76.7)</td>
</tr>
<tr>
<td>Unintentional discrepancies</td>
<td>Intervention</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>--------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. UDs</td>
<td>No. patients</td>
<td>No. per patient</td>
</tr>
<tr>
<td>Admission</td>
<td>255</td>
<td>95</td>
<td>2.80</td>
</tr>
<tr>
<td>Resolved during hospital stay</td>
<td>250</td>
<td>95</td>
<td>2.74</td>
</tr>
<tr>
<td>Remaining at discharge</td>
<td>2</td>
<td>91</td>
<td>0.02</td>
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### Table 3  Comparison of outcome measures

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<tr>
<th>Outcome</th>
<th>Measure</th>
<th>N</th>
<th>Intervention</th>
<th>N</th>
<th>Control</th>
<th>Mean difference (SE of the difference)</th>
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<tr>
<td>Length of stay (hours)</td>
<td>Geometric Mean (95% CI)</td>
<td>95</td>
<td>99.6 (76.59 to 129.63)</td>
<td>102</td>
<td>109.3 (87.0 to 137.3)</td>
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<tr>
<td></td>
<td>Median (range)</td>
<td>95</td>
<td>94.0 (12 – 1077)</td>
<td>102</td>
<td>117 (13 - 1546)</td>
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</tr>
<tr>
<td></td>
<td>Arithmetic mean (SD)</td>
<td>95</td>
<td>224.8 (293.1)</td>
<td>102</td>
<td>203.9 (246.8)</td>
<td>20.84 (38.75)</td>
</tr>
<tr>
<td>Hospital readmissions</td>
<td>No. (%)</td>
<td>95</td>
<td>30 (31.6)</td>
<td>101</td>
<td>37 (36.6)</td>
<td></td>
</tr>
<tr>
<td>Hospital readmissions (emergency)</td>
<td>No. (%)</td>
<td>95</td>
<td>17 (17.7)</td>
<td>101</td>
<td>27 (26.7)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>No. (%)</td>
<td>95</td>
<td>6 (6.3)</td>
<td>95</td>
<td>8 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Quality of life Visual Analogue Scale change from baseline (high score better)</td>
<td>Mean (SD)</td>
<td>63</td>
<td>5.64 (23.6)</td>
<td>68</td>
<td>7.15 (26.2)</td>
<td>1.51 (4.36)</td>
</tr>
</tbody>
</table>
References


2. The University of Sheffield SoHaRRS. A systematic review of the effectiveness and cost-effectiveness of interventions aimed at preventing medication error (medicines reconciliation) at hospital admission. NICE. 2009.


### CONSORT 2010 checklist of information to include when reporting a randomised trial*

<table>
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<tr>
<th>Section/Topic</th>
<th>Item No</th>
<th>Checklist item</th>
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<td>Identification as a randomised trial in the title</td>
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<tr>
<td></td>
<td>1b</td>
<td>Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)</td>
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<tr>
<td><strong>Introduction</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>2a</td>
<td>Scientific background and explanation of rationale</td>
<td>4</td>
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<tr>
<td></td>
<td>2b</td>
<td>Specific objectives or hypotheses</td>
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<tr>
<td><strong>Methods</strong></td>
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<tr>
<td>Trial design</td>
<td>3a</td>
<td>Description of trial design (such as parallel, factorial) including allocation ratio</td>
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<tr>
<td>Participants</td>
<td>4a</td>
<td>Eligibility criteria for participants</td>
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<tr>
<td></td>
<td>4b</td>
<td>Settings and locations where the data were collected</td>
<td>5</td>
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<tr>
<td>Interventions</td>
<td>5</td>
<td>The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
<td>11</td>
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<tr>
<td>Outcomes</td>
<td>6a</td>
<td>Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed</td>
<td>6</td>
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<tr>
<td></td>
<td>6b</td>
<td>Any changes to trial outcomes after the trial commenced, with reasons</td>
<td>N/A</td>
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<tr>
<td>Sample size</td>
<td>7a</td>
<td>How sample size was determined</td>
<td>7</td>
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<td></td>
<td>7b</td>
<td>When applicable, explanation of any interim analyses and stopping guidelines</td>
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<tr>
<td><strong>Randomisation:</strong></td>
<td></td>
<td></td>
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<tr>
<td>Sequence</td>
<td>8a</td>
<td>Method used to generate the random allocation sequence</td>
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<tr>
<td>generation</td>
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<td>Type of randomisation; details of any restriction (such as blocking and block size)</td>
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<tr>
<td>Allocation</td>
<td>9</td>
<td>Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
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<tr>
<td>concealment mechanism</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Implementation</td>
<td>10</td>
<td>Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
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<tr>
<td>Blinding</td>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those</td>
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*For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
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<td>If relevant, description of the similarity of interventions</td>
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<td><strong>Results</strong></td>
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<tr>
<td>13a</td>
<td>For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome</td>
<td>8</td>
</tr>
<tr>
<td>13b</td>
<td>For each group, losses and exclusions after randomisation, together with reasons</td>
<td>8</td>
</tr>
<tr>
<td>14a</td>
<td>Dates defining the periods of recruitment and follow-up</td>
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<td>14b</td>
<td>Why the trial ended or was stopped</td>
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<tr>
<td>15</td>
<td>A table showing baseline demographic and clinical characteristics for each group</td>
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<tr>
<td>16</td>
<td>For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups</td>
<td>15</td>
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<tr>
<td>17a</td>
<td>For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)</td>
<td>15</td>
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<tr>
<td>17b</td>
<td>For binary outcomes, presentation of both absolute and relative effect sizes is recommended</td>
<td>15</td>
</tr>
<tr>
<td>18</td>
<td>Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory</td>
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</tr>
<tr>
<td>19</td>
<td>All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)</td>
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<tr>
<td><strong>Discussion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses</td>
<td>9</td>
</tr>
<tr>
<td>21</td>
<td>Generalisability (external validity, applicability) of the trial findings</td>
<td>9</td>
</tr>
<tr>
<td>22</td>
<td>Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence</td>
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<tr>
<td><strong>Other information</strong></td>
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<td>23</td>
<td>Registration number and name of trial registry</td>
<td>Info submitted online</td>
</tr>
<tr>
<td>24</td>
<td>Where the full trial protocol can be accessed, if available</td>
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<td>25</td>
<td>Sources of funding and other support (such as supply of drugs), role of funders</td>
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*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
Pharmacist provided medicines reconciliation within 24 hours of admission and on discharge: A randomised controlled pilot study

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<td>Date Submitted by the Author:</td>
<td>07-Nov-2016</td>
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<td>Complete List of Authors:</td>
<td>Cadman, Brit; Cambridge University Hospitals NHS Foundation Trust, Pharmacy Wright, David; University of East Anglia, School of Pharmacy Bale, Amanda; Cambridge University Hospitals NHS Foundation Trust, Pharmacy Barton, Garry; University of East Anglia, Norwich Medical School Hammad, Eman; University of Jordan Desborough, James; University of East Anglia, School of Pharmacy Holland, Richard; University of East Anglia, Norwich Medical School Howe, Helen; Cambridge University Hospitals NHS Foundation Trust, Pharmacy Nunney, Ian; University of East Anglia, Norwich Medical school Irvine, Lisa; University of East Anglia, Norwich Medical School</td>
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Pharmacist provided medicines reconciliation within 24 hours of admission and on discharge: A randomised controlled pilot study

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⁶ Patient and Public Involvement Representative

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MeSH words: Medication reconciliation, cost-effectiveness, pharmacy, randomised controlled trial, pilot study.

Word count: 4165 excluding figures, tables and references
Abstract

Background
The UK government currently recommends that all patients receive medicines reconciliation (MR) from a member of the pharmacy team within 24 hours of admission and subsequent discharge. The cost-effectiveness of this intervention is unknown. A pilot study to inform the design of a future randomised controlled trial to determine effectiveness and cost-effectiveness of a pharmacist delivered service was undertaken.

Method
Patients were recruited seven days a week from five adult medical wards in one hospital over a 9 month period and randomised using an automated system to intervention (MR within 24 hours of admission and at discharge) or usual care which may include MR (control). Recruitment and retention rates were determined. Length of stay (LOS), quality of life (EQ-5D-3L), unintentional discrepancies (UDs) and emergency re-admission (ER) within 3 months were tested as outcome measures. The feasibility of identifying and measuring intervention associated resources was determined.

Result
200 patients were randomised to either intervention or control. Groups were comparable at baseline. 95 (99%) of patients in the intervention received MR within 24 hours, whilst 62 (60.8%) of control patients received MR at some point during admission. The intervention resolved 250 of the 255 UDs identified at admission. Only 2 UDs were identified in the intervention group at discharge compared with 268 in the control. The median LOS was 94 hours in the intervention arm and 118 hours in the control, with ER rates of 17.9% and 26.7%, respectively. Assuming 5% loss to follow up 1120 patients (560 in each arm) are required to detect a 6% reduction in 3 month ER rates.

Conclusions
The results suggest that changes in outcome measures resulting from MR within 24 hours were in the appropriate direction and readmission within 3 months is the most appropriate primary outcome measure. A future study to determine cost-effectiveness of the intervention is feasible and warranted.

Strengths and limitations
- Pilot randomised controlled trial
- Intervention fidelity enhanced through competency assessment of medicine reconciliation providers
- Robust process for identifying unintentional discrepancies at each stage developed to prevent results contamination
- Pragmatic design and therefore elements of the intervention found within the control arm
- Limited response to request for patient data 3 months post-discharge
Background

Medicines Reconciliation (MR) is defined by the World Health Organisation as ‘the formal process in which healthcare professionals partner with patients to ensure accurate and complete medication information transfer at the interfaces of care’. (1) Researchers have identified unintentional error rates within hospital prescriptions on admission of between 30-70% (2-5) and these can include omission of usual medicines, prescription of incorrect dosages and addition of medicines which have not been previously prescribed. The majority of these errors are believed to result from deficiencies in the MR process with such errors known to contribute to patient morbidity and mortality and increase the length of hospital stay (LOS). (6-10)

Consequently, within the UK, patient safety guidance issued by the National Patient Safety Agency (NPSA) and the National Institute of Health and Care Excellence (NICE) recommended that policies for MR should be implemented in hospitals for all adult patient admissions, and that pharmacy should be involved in the MR process within 24 hours of admission. (11) NICE guidance on pharmacy involvement was based primarily on one randomised controlled trial (RCT) which demonstrated that the inclusion of the pharmacist in MR reduced the error rate from 44% to 19%. (2) 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.

Recent systematic reviews of hospital based medicines reconciliation practices consistently demonstrate a reduction in medicine discrepancies, however this has not been shown to result in reductions in post-discharge healthcare utilisation. (13, 14) When considering only pharmacist-led medicines reconciliation interventions a 19% reduction in the rate of all cause readmissions was seen but similarly pooled data on mortality and composite readmission and emergency department visit did not find in favour of either pharmacist-led intervention or usual care. (15)

With the significant resources required for pharmacists to deliver medicines reconciliation services it is not adequate to demonstrate reduction in errors (which may or may not result in adverse drug events), it is also important in resource limited health systems to show that such investment constitutes value for money. There is currently a recognised lack of evidence supporting the cost-effectiveness of medicines reconciliation interventions provided by pharmacists. (16) A model built in 2008 to estimate the likely cost-effectiveness of preventing medication error at hospital admission using medicines reconciliation suggested that a pharmacist based intervention is likely to be cost-effective but was based solely on USA error data and made assumptions concerning the severity of errors prevented. (17)

Despite national guidance few hospitals are providing MR as envisioned by NICE for all patient admissions. (18) Thus, it would appear that further high quality evidence which demonstrates cost-effectiveness is required to ensure that resources are appropriately allocated to this service in order to meet national recommendations. The most suitable approach to determine the cost-effectiveness of a complex intervention such as medicines reconciliation is to perform a RCT which collates data on cost from the appropriate perspective and outcomes which are most proximal to the intervention. Within the UK it is additionally necessary to collect data on quality of life and mortality to enable the cost per quality adjusted life year to be estimated. Recent guidance however suggests that before an RCT of such nature is undertaken feasibility testing and piloting are required. (19)

Aims

The aim of this study was therefore to pilot a randomised controlled trial to inform the design of a future definitive study to determine the clinical and cost-effectiveness of pharmacy providing a full MR service on admission and at discharge. The objectives of the pilot study were to

- identify the most suitable outcome measure for a future definitive trial with respect to proximity and response to the intervention and quality of data obtained
- determine potential recruitment and retention rates
• develop and test the process for measuring resource utilisation associated with the intervention and use of other NHS services

Method

Study design and location
The trial was randomised controlled pilot study undertaken at Cambridge University Hospitals NHS Foundation Trust (CUHFT) on five adult medical wards from a range of medical specialities where patients did not routinely receive MR from a pharmacist within 24 hours of admission. One similar ward was identified as a “backup”, in the eventuality that one of the study wards was closed for any reason (e.g. norovirus outbreak) during the recruitment period.

Intervention
A standard operating procedure (SOP) based on hospital guidelines, outlined in Figure 1, was used to deliver MR by a trained medicines reconciliation pharmacist (MRP) within 24 hours of admission (including weekends) and at the point of transfer of care out of hospital, or as soon as possible following patient discharge from hospital to the next care provider. The five MRPs, all clinical pharmacists employed within the hospital, covered for each other’s holidays, sick leave and absences wherever possible.

MRPs recorded all unintentional discrepancies (UDs), defined as differences between patient records with no identifiable rationale, they identified between the information they collated and the inpatient medication chart on admission and again any differences between the inpatient chart and discharge letter. MRPs followed up on all identified UD to ensure that they were addressed prior to discharge.

Control
Patients in the control arm received usual care which may or may not consist of medicines reconciliation and where it may not have occurred within 24 hours and could either be delivered by a pharmacist or pharmacy technician. The MRPs within the intervention arm did not deliver MR to control patients and the SOP used for study intervention purposes was not automatically followed within the control arm. For the purposes of the study all MR details regarding interventions undertaken within the control arm were recorded and costed.

Intervention fidelity
To enhance intervention fidelity all MRPs were observed by the Principal Investigator (PI) on at least 3 occasions to confirm adherence to the SOP. All MRPs had provided MR to more than 30 patients in the year previous to delivering the intervention for the trial.

Recruitment
A recruitment target of 200 patients was set for the nine-month pilot phase. Study wards were visited every morning by the research assistant (RA) during the study period to identify potential participants. 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. Patients were recruited based on the following inclusion and exclusion criteria.

Inclusion criteria:
• Adult (≥18 years of age)
• Admitted with at least one prescribed medicine to one of the five medical wards
• Patient had not already received MR from the pharmacy team as part of routine pharmaceutical input at the time of recruitment
• Identified from hospital computer system as having been admitted straight from the Emergency Department (ED) to one of the five participating wards within the previous 24 hours
With the intervention required to be delivered within 24 hours of admission, patients were given a maximum of 2 hours to consider whether they wished to participate. Intervention patients received MR in accordance with the SOP. Information obtained by the RA for the purposes of the study was given to the MRP pharmacist prior to the visit to prevent duplication of effort and to ensure the patient was not interviewed for the same information twice.

Randomisation was performed utilising the Norwich Clinical Trials Unit automated service with patients stratified by ward. When wards were later closed for infection control reasons, participants on the “backup” ward were randomised and stratified as if they had entered the closed ward.

Patients randomised to the control group received usual care; this may have included elements of MR by members of the pharmacy team and in some cases may have occurred within 24 hours of admission but post-randomisation. Whilst this may have affected patients in the control arm an intention to treat analysis was performed and consequently for the purpose of the analysis patients they remained in their allocated arm.

Outcome measures
Although undertaken as a pilot study with study aims to identify the most suitable outcome measure, length of stay (LOS) was nominally selected as the primary outcome measure for this pilot trial. Secondary outcome measures were unplanned (emergency) re-admission at 3 months, quality of life (EQ-5D-3L) and unintentional discrepancies.

Data collection
To enable comparison of intervention and control groups, age, gender, primary reason for admission, all co-morbidities and the admission ward was recorded. Additionally consented patients or their third party consultees completed a quality of life score (EQ-5D-3L) (20) on admission, including the related visual analogue scale (VAS).

LOS, reported in hours, was calculated as the difference in time from arrival at the hospital to the time of discharge as recorded in the hospital information system (HISS). Unplanned re-admissions to the intervention hospital within the 3 months post-discharge were also obtained from HISS. EQ-5D-3L responses were also obtained via postal survey 3 months post-discharge, allowing the calculation of Quality Adjusted Life Years (QALYs) (21) in the subsequent economic evaluation.

Unintentional discrepancy identification
To enable the identification of UDs the following information was photocopied by the research associate (RA) for all consented patients (both intervention and control) and stored securely:

- All versions of the inpatient medication chart(s) and discharge letters,
- Medical notes during admission
- GP medication list on admission
- GP medication list at 3 month post discharge (when received from GP surgery)
- Any additional medicines related information brought in by the patient on admission e.g. copies of labels from patient medicines, handwritten or typed medicine lists.

The RA was a trained nurse and consequently was experienced in medical data collation and extraction.

3 months post discharge the stored information was used to develop an ‘accurate medication list’ for the control arm patients by the research team on admission and at discharge. These were then compared with the inpatient chart on admission and discharge letter to identify any discrepancies. Medical notes were subsequently reviewed, unblinded to group allocation, to enable differentiation between those which were unintentional i.e. discrepancies which could not be explained from the information available and those which were intentional.

The GP medication list obtained 3 months post discharge (where available) was used to enable the identification of discrepancies which still remained at 3 months. Without access to
GP medical notes it was not possible to establish whether identified discrepancies were unintentional.

All potential discrepancies which were identified at the 3 month point as having translated into the patient notes were reported to the patient’s GP.

Resource use
The time taken by the pharmacy team to deliver the MR was monitored in both the intervention and control group (if applicable). Additionally, the following items were requested in both groups:

- Time in hospital (Length of stay)
- Medication (in patient medication and GP medication list at 3 months)
- Re-hospitalisations
- Other health care contacts

With the exception of the final item, which included all health professional contacts and was requested from the participant at 3 months post discharge, these were extracted from medical records.

Sample size calculation
As a pilot study a formal power calculation was not performed. The consequences for the precision of the primary outcome variable (LOS) of the choice of sample-size were however estimated. Summary statistics on LOS taken from a study undertaken at St James Hospital, Dublin (22) gave quartiles for two groups as (3, 7, 5) and (2, 5, 12) days. To derive an estimate of variability from this, an underlying log-normal distribution was assumed, which is consistent with the position of the medians, and its standard deviation estimated using the geometric mean of the ratios between the upper and lower quartiles. This produced an estimated SD of 1.26 which implied that a comparison between 2 groups of 100 patients, would provide an expected half-width for the 95% confidence interval of the difference between group-means (on the natural log scale) of 0.35. Translated back to the confidence interval for the ratio of average length of stay between the intervention and control groups would extend by a factor of about 1.4 either side of the point estimate.

Data analysis
As a pilot study descriptive statistics were utilised to determine the suitability of the different outcome measures and report the variation in the differences in order to determine a sample size for a future randomised controlled trial. Similarly, completion rates are reported for each source of resource use data and the EQ-5D-3L.

The primary outcome variable, length of stay, was reported using median, arithmetic mean and geometric mean. The rate of Trust re-admissions, Trust emergency re-admissions and mortality are also reported for both arms, along with the mean change in the VAS from the EQ-5D-3L.

Results
Nine hundred and nineteen patients were assessed for eligibility of which 224 did not meet inclusion criteria. 200 out of 310 patients who were subsequently approached by the RA consented to take part in the study (Figure 2). Of those patients identified as potentially eligible but not approached this was primarily because either the nurse in charge of the ward advised that the patient was not suitable to be approached or that the end of the 24 hour window for intervention was due to expire.

Recruitment took place between July 2012 and April 2013 (9 months and 2 weeks), resulting in a recruitment rate of 5.2 patients per seven days.

There was one post-randomisation exclusion in each arm (they were subsequently found not to meet the inclusion criteria), and were accordingly excluded from all analyses. Table 1 thereby summarises the characteristics of the remaining 198 participants (96 intervention 102 control). The groups were broadly comparable.
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. The time taken by the pharmacist to deliver the intervention was recorded for the remaining 95 intervention participants, where the mean total time was 48.6 minutes (range 2 to 195 minutes). In the control group 62 (60.8%) participant received some form of medicines reconciliation, 31 (30.4%) from a pharmacist (mean reported time 15 minutes) and 31 (30.4%) from a pharmacy technician (mean reported time 12 minutes) 25 (24.5%) control patients received MR within the 24 hour window.

During the initial hospital admission three participants died, with a further 11 deaths during the three months follow-up period (see Figure 2). In total 6 intervention and 8 control patients died during the trial period (p=0.78, Fisher’s Exact). Additionally, in the control arm, one participant was lost to follow up (address not known) and one participant withdrew. After taking account of the 1 patient who did not receive the MR and a further loss to follow-up in the intervention arm, this left a total of 88 available cases in the intervention arm and 92 available cases in the control arm at final assessment point. In terms of outcomes, there was complete data available on LOS and re-admission data.

Table 2 provides a summary of the unintentional discrepancies which were identified at each stage. 16 (16%) intervention patients had no discrepancies at admission and discharge, compared to 12 (12%) control patients. Overall, 2 UDs were known to remain at discharge in the intervention arm compared with 268 in the control group. Neither of the UDs in the intervention arm identified at discharge were present at 3 months.

One hundred and fifty four unintentional discrepancies identified in the control arm were potentially related to medicines to be prescribed post-discharge i.e. the remainder related to medicines prescribed during admission only. Due to the limited number of GP records provided at 3 months data were only available for 82 (53.2%) unintentional discrepancies in the control arm at 3 months and 37 out of the original 154 (24%) were found from the medical records provided to have been propagated into the patient notes.

Table 3 provides a comparison of patient outcomes for the intervention and control group. The results suggest that LOS, mortality and rehospitalisation rates tend to be lower in the intervention arm although statistical significance was not demonstrated as 95% Confidence Intervals overlapped. Based on those who responded, both groups had a higher mean quality of life (based on the VAS) at the 3 month follow up with improvement higher in the control arm. This difference between groups was not significant.

With regard to the response rates for the resource use data there were complete data available (for those upon whom it was requested) for length of stay, medication data as part of the original admission, re-admissions (to the same hospital) and the intervention pharmacist times. Of the 62 controls for whom pharmacist/pharmacy technician review occured the times were missing for N=27. At 3 month follow-up, medication data were retrieved from GPs for 86 participants (94.5% of those from whom it was requested) in each arm and 133 participants completed and returned both the EQ-5D-3L and the health resource use questionnaires (66 Intervention, 67 Control) (73.5% of those requested from all living participants).

Based on the pilot data we calculate that for a full trial 1120 patients would need to be recruited to detect a 6% reduction (conservative assumption, one standard error below 9% reduction seen) in 3 month unplanned re-admission rates from a starting point of 26% with 90% power, using a 5% significance level and assuming 5% loss to follow up.
Discussion

The results from this study which was performed to inform the design of a future randomised controlled trial suggest that even though medicines reconciliation activities are taking place such a trial is feasible with reasonable recruitment and retention rates and that both cost and outcome data can be effectively obtained.

We consider that emergency rehospitalisation within 3 months would be the most appropriate primary outcome measure for such a trial, as unlike the other outcome measures tested, it reflects all of the MR activity which occurs in both secondary and primary care. Furthermore, data collection was complete and this is a patient-orientated outcome, unlike medication errors which whilst representing a patient safety issue are a measure of the prescribing process.

Due to the need to recruit patients before they received MR as usual care this reduced the generalisability of the sample with all of those who had already received MR being automatically excluded. This was further compounded by recruitment activities which were focussed towards mornings.

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.

The average time spent on the intervention found within this study was very similar to that reported in a MR time and motion study(23) but three times greater than that in the control arm. 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. It has been suggested that organisations are probably unlikely to repeat the benefits from MR services reported in the literature if there are deficiencies in intervention intensity and breadth.(24) The results from the control arm of this study support this assertion and suggest that if MR of a similar nature to that seen in the intervention arm was to be shown to be cost-effective then this would require significantly more pharmacist time.

The proportion of patients screened for eligibility and eventually recruited to the study was 20% and this could have been improved by increasing the number of weekends covered (from 80% to 100%). Although some patients were not suitable for inclusion in the study as they had already been reviewed by a member of the pharmacy team prior to being approached by the RA, there was a sufficient number of patients available for recruitment.

When identifying unintentional discrepancies, we have assumed that 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.

The process of collating all medicines related data at different time points and sealing it until 3 months post discharge provides an opportunity to identify discrepancies without adversely affecting the intervention. Whilst the identification of unintentional discrepancies should be undertaken blind of allocation the resources required for this may not be warranted when considering that the intentional or unintentional nature of the discrepancy cannot always be accurately determined.
Considering evidence published post-study completion, limiting the study population to those over the age of 70 and including a post-discharge telephone call as part of the intervention may have further enhanced the intervention. (13)

In line with previous research the intervention prevented a large number of unintentional medicines related discrepancies both during admission and post-discharge. (3-6) The data obtained suggests that just less than a quarter of unintentional discrepancies identified at discharge were found to actually translate into primary care records at three months. Whilst reasons for non-translation were not elucidated the research suggests that the use of number of unintentional discrepancies at discharge as an outcome measure may over-emphasise the problem.

Not all primary care medication lists were made available to researchers and approaches to addressing this will require consideration for a future definitive study. Utilising data on 'unplanned readmission at 3 months' would seem to be the most appropriate primary outcome measure for a future definitive study as it is a patient orientated outcome which is most likely to reflect the effect of errors which occur at all stages of the process. Similar to hospital readmission, LOS is a cost which would be captured in any cost-effectiveness analysis. LOS was however found to be largely skewed by a small number of individuals who were admitted for extended periods. Furthermore, it is not affected by errors which translate into primary care i.e. does not reflect the full impact of the service. Within the UK hospitals are penalised for unplanned readmissions within one month of discharge and therefore collection of this data may also be warranted for a UK based definitive study.

Unplanned readmission has been used as a primary outcome measure within other similar MR trials (25-29). Whilst differences in unplanned readmission at three months have been demonstrated, (28, 29) this has frequently not been the case at either one or six months. (25-27) Within the first month patients may still be using the medication they were discharged with and consequently this may lessen the impact of errors on the discharge letter resulting from incorrect translation into primary care. Kwan et al. after systematically reviewing the literature suggest that unplanned readmission data should probably be collected for more than 30 days post-discharge. (14) Unplanned readmission at six months will be affected by more factors unrelated to the index admission than at 3 months and therefore it may be more difficult to identify the impact of MR intervention using this outcome measure.

Quality of data collection with respect to LOS, mortality and readmission rates was high as this information was available from hospital records. Resource utilisation data and quality of life scores were however only available for two thirds of participants at follow up. Consequently researchers powering a definitive study on readmission rate will need to consider the possibility of there being more missing data for the cost-effectiveness analysis and imputation of missing data (30) may be necessary to address this.

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. However, it was conducted as an RCT, conforming to expected standards and consequently it can be assumed that it would be possible to perform a full scale RCT in the future. An internal pilot would be warranted in such a trial as the trial should be multi-centre in nature and consequently local variations in recruitment rates and service delivery would require identification and appropriate local adaptation. Additionally, costs related to service delivery may differ between settings and consequently time for service delivery would require estimation.

The pilot study has shown that it is feasible to perform an RCT to determine the effectiveness and cost-effectiveness of a pharmacist MR within 24 hours of admission and again at discharge. This study has demonstrated that this form of intervention does appear to reduce medication errors at discharge, and may reduce LOS and hospital readmissions. We consider that unplanned readmission at 3 months is the most suitable primary outcome measure but LOS, errors, mortality and quality of life should be captured.
Additionally a thorough process evaluation is warranted in order provide a more complete understanding of the intervention. Pharmacists delivering the intervention arm within a definitive study should follow an SOP and be trained to undertake the role to ensure standardisation in delivery. Whilst the results of this pilot emulate other studies where prescribing errors were reduced in the intervention arm 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.

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Contributors:
BC, EH, DW, JD, RH participated in the conception and design of this study. AB, BC, DW, GB, IN, LI participated in the analysis of the data and interpretation of the results AB, BC, DW drafted the article and all other authors performed critical review of the article. All authors approved the submission of this article

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Competing interests:
None

Ethics approval:
Ethical approval was received on 14th June 2012 from NRES Committee East of England - Essex Research Ethics Committee. Reference number: 12/44/0143

Provenance and peer review
The trial was registered on 5th August 2012: ISRCTN23949491
The trial received competitive funding from NIHR Research for Patient Funding stream and was peer reviewed as part of this process.
Figure 1  Outline of service standard operating procedure

Admission

- Patient interviewed to confirm allergy status and medicines being taken
- GP letter/fax reviewed to confirm allergy status and medicines prescribed
- Medical notes reviewed to confirm any intentional medication changes due to clinical status of patient
- Other sources of information may have been used depending on availability and relevance to current admission by virtue of the date, and included
  o previous electronic discharge letter
  o clinic letter
  o patient’s own drugs (PODs)
  o patients relative or carer
  o nursing home record
  o medication administration record (MAR)
  o modified dosage system (MDS)
- An accurate medication list was documented in the medical notes by the intervention pharmacist

Discharge

- Discharge letter compared with the final drug chart to ensure correct
- Medical notes reviewed
- Changes to medicines field on the electronic system was completed by the intervention pharmacist to communicate intentional medication changes to the GP
- All medicines were added to the discharge letter to ensure a complete record at the point of transfer of care
Figure 2  Consort diagram

Enrolment

Assessed for eligibility (n=919)

Excluded (n=719)
  • Not meeting inclusion criteria (n=224)
  • Declined to participate (n=110)
  • Other reasons (n=385)

Randomised (n=200)

Excluded post-randomisation (n=1 #95)
  Not meeting inclusion

Intervention arm (n=96)
  • Received intervention < 24 hr (n=95)
  • Did not receive intervention as > 24 hr (n=1) #75

Control arm (n=102)
  • < 24 hour by pharmacist (n=13)
  • < 24 hour by technician (n=22)
  • > 24 hour by pharmacist (n=18)
  • > 24 hour by technician (n=9)
  • No MR performed (n=40)

Allocation

Discharge follow up

Lost to follow up (n=0) Death (n=2) #108 #136

3 month follow up

Lost to follow up (n=1) #70 Withdrawn (n=0) Death (n=4) #51, 68, 82, 97

Data availability

Complete self-reported cost data (n=66)
  EQ5D data available at 3 months (incl. deaths) (n=72)
  Medication data received from GPs at 3 months (n=78)
  Medication data not provided at 3 months (n=12 plus n=6 RPs)

Complete self-reported cost data (n=66)
  EQ5D data available at 3 months (incl. deaths) (n=75)
  Medication data received from GPs at 3 months (n=85)
  Medication data not provided at 3 months (n=9 plus n=8 RPs)
Table 1  Comparison of demographics at baseline:

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Measure</th>
<th>Intervention (n=96)</th>
<th>Control (n=102)</th>
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</thead>
<tbody>
<tr>
<td>Female</td>
<td>No. (%)</td>
<td>45 (46.9)</td>
<td>60 (58.8)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>67.6 (19.0)</td>
<td>65.4 (20.2)</td>
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<td>Regular medicines</td>
<td>Mean (SD)</td>
<td>5.84 (4.07)</td>
<td>6.67 (4.64)</td>
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<tr>
<td>As required medicines</td>
<td>Mean (SD)</td>
<td>0.85 (2.08)</td>
<td>0.95 (2.53)</td>
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<tr>
<td>Ward</td>
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</tr>
<tr>
<td>1</td>
<td>No. (%)</td>
<td>26 (26.8)</td>
<td>27 (26.2)</td>
</tr>
<tr>
<td>2</td>
<td>No. (%)</td>
<td>30 (30.9)</td>
<td>30 (29.1)</td>
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<tr>
<td>3</td>
<td>No. (%)</td>
<td>10 (10.3)</td>
<td>9 (8.7)</td>
</tr>
<tr>
<td>4</td>
<td>No. (%)</td>
<td>14 (14.4)</td>
<td>16 (15.5)</td>
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<tr>
<td>5</td>
<td>No. (%)</td>
<td>16 (16.4)</td>
<td>14 (13.5)</td>
</tr>
<tr>
<td>6</td>
<td>No. (%)</td>
<td>1 (1.03)</td>
<td>7 (6.8)</td>
</tr>
<tr>
<td>EQ5D Quality of life (Visual Analogue Scale)</td>
<td>Mean (SD)</td>
<td>55.9 (23.2)</td>
<td>54.7 (23.5)</td>
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<td>Reason for admission</td>
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<tr>
<td>Lower respiratory tract infection</td>
<td>No. (%)</td>
<td>9 (9.2)</td>
<td>11 (10.7)</td>
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<tr>
<td>Troponin –ve chest pain</td>
<td>No. (%)</td>
<td>7 (7.2)</td>
<td>4 (3.9)</td>
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<td>Heart failure</td>
<td>No. (%)</td>
<td>2 (2.1)</td>
<td>5 (4.9)</td>
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<tr>
<td>Exacerbation Chronic Obstructive Pulmonary Disease</td>
<td>No. (%)</td>
<td>4 (4.1)</td>
<td>3 (2.9)</td>
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<tr>
<td>Other</td>
<td>No. (%)</td>
<td>73 (75)</td>
<td>79 (76.7)</td>
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Table 2  Comparison of unintentional discrepancies (UDs)

<table>
<thead>
<tr>
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<th>Intervention</th>
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<th>Control</th>
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<tr>
<td></td>
<td>No. UDs</td>
<td>No. patients</td>
<td>No. per patient</td>
<td>No. UDs</td>
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<td>Admission</td>
<td>255</td>
<td>95</td>
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<td>Resolved during hospital stay</td>
<td>250</td>
<td>95</td>
<td>2.74</td>
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<tr>
<td>Remaining at discharge</td>
<td>2</td>
<td>91</td>
<td>0.02</td>
<td>268</td>
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Table 3  Comparison of outcome measures

<table>
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<tr>
<th>Outcome</th>
<th>Measure</th>
<th>N</th>
<th>Intervention</th>
<th>N</th>
<th>Control</th>
<th>Mean difference (SE of the difference)</th>
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</thead>
<tbody>
<tr>
<td>Length of stay (hours)</td>
<td>Geometric Mean (95% CI)</td>
<td>95</td>
<td>99.6 (76.59 to 129.63)</td>
<td>102</td>
<td>109.3 (87.0 to 137.3)</td>
<td>20.84 (38.75)</td>
</tr>
<tr>
<td></td>
<td>Median (range)</td>
<td>95</td>
<td>94.0 (12 – 1077)</td>
<td>102</td>
<td>117 (13 - 1546)</td>
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<tr>
<td></td>
<td>Arithmetic mean (SD)</td>
<td>95</td>
<td>224.8 (293.1)</td>
<td>102</td>
<td>203.9 (246.8)</td>
<td>20.84 (38.75)</td>
</tr>
<tr>
<td>Hospital readmissions</td>
<td>No. (%)</td>
<td>95</td>
<td>30 (31.6)</td>
<td>101</td>
<td>37 (36.6)</td>
<td></td>
</tr>
<tr>
<td>Hospital readmissions (emergency)</td>
<td>No. (%)</td>
<td>95</td>
<td>17 (17.9)</td>
<td>101</td>
<td>27 (26.7)</td>
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<tr>
<td>Mortality</td>
<td>No. (%)</td>
<td>95</td>
<td>6 (6.3)</td>
<td>95</td>
<td>8 (7.8)</td>
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<tr>
<td>Quality of life Visual Analogue Scale</td>
<td>Mean (SD)</td>
<td>63</td>
<td>5.64 (23.6)</td>
<td>68</td>
<td>7.15 (26.2)</td>
<td>1.51 (4.36)</td>
</tr>
</tbody>
</table>
References


2. The University of Sheffield SoHaRRS. A systematic review of the effectiveness and cost-effectiveness of interventions aimed at preventing medication error (medicines reconciliation) at hospital admission. NICE. 2009.


**CONSORT 2010 checklist of information to include when reporting a randomised trial**

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item No</th>
<th>Checklist item</th>
<th>Reported on page No</th>
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<tr>
<td>1a</td>
<td>Identification as a randomised trial in the title</td>
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<tr>
<td>1b</td>
<td>Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)</td>
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<tr>
<td><strong>Introduction</strong></td>
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<tr>
<td>2a</td>
<td>Scientific background and explanation of rationale</td>
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<tr>
<td>2b</td>
<td>Specific objectives or hypotheses</td>
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<tr>
<td><strong>Methods</strong></td>
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<td>3a</td>
<td>Description of trial design (such as parallel, factorial) including allocation ratio</td>
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<td>3b</td>
<td>Important changes to methods after trial commencement (such as eligibility criteria), with reasons</td>
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<tr>
<td>4a</td>
<td>Eligibility criteria for participants</td>
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<td>4b</td>
<td>Settings and locations where the data were collected</td>
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<td>5</td>
<td>The interventions for each group with sufficient details to allow replication, including how and when they were actually administered</td>
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<td><strong>Outcomes</strong></td>
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<td>Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed</td>
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<td>How sample size was determined</td>
<td>7</td>
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</tr>
<tr>
<td>7b</td>
<td>When applicable, explanation of any interim analyses and stopping guidelines</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>8a</td>
<td>Method used to generate the random allocation sequence</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>8b</td>
<td>Type of randomisation; details of any restriction (such as blocking and block size)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>11a</td>
<td>If done, who was blinded after assignment to interventions (for example, participants, care providers, those</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Section</td>
<td>Item</td>
<td>Description</td>
<td>Score</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Assessing outcomes</td>
<td>11b</td>
<td>If relevant, description of the similarity of interventions</td>
<td>N/A</td>
</tr>
<tr>
<td>Statistical methods</td>
<td>12a</td>
<td>Statistical methods used to compare groups for primary and secondary outcomes</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>12b</td>
<td>Methods for additional analyses, such as subgroup analyses and adjusted analyses</td>
<td>N/A</td>
</tr>
<tr>
<td>Results</td>
<td>13a</td>
<td>For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>13b</td>
<td>For each group, losses and exclusions after randomisation, together with reasons</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>14a</td>
<td>Dates defining the periods of recruitment and follow-up</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>14b</td>
<td>Why the trial ended or was stopped</td>
<td>N/A</td>
</tr>
<tr>
<td>Baseline data</td>
<td>15</td>
<td>A table showing baseline demographic and clinical characteristics for each group</td>
<td>13</td>
</tr>
<tr>
<td>Numbers analysed</td>
<td>16</td>
<td>For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups</td>
<td>15</td>
</tr>
<tr>
<td>Outcomes and estimation</td>
<td>17a</td>
<td>For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>17b</td>
<td>For binary outcomes, presentation of both absolute and relative effect sizes is recommended</td>
<td>15</td>
</tr>
<tr>
<td>Ancillary analyses</td>
<td>18</td>
<td>Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory</td>
<td>N/A</td>
</tr>
<tr>
<td>Harms</td>
<td>19</td>
<td>All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)</td>
<td>N/A</td>
</tr>
<tr>
<td>Discussion</td>
<td>20</td>
<td>Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses</td>
<td>9</td>
</tr>
<tr>
<td>Generalisability</td>
<td>21</td>
<td>Generalisability (external validity, applicability) of the trial findings</td>
<td>9</td>
</tr>
<tr>
<td>Interpretation</td>
<td>22</td>
<td>Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence</td>
<td>10</td>
</tr>
<tr>
<td>Other information</td>
<td>23</td>
<td>Registration number and name of trial registry</td>
<td>Info submitted online</td>
</tr>
<tr>
<td>Protocol</td>
<td>24</td>
<td>Where the full trial protocol can be accessed, if available</td>
<td>Info submitted online</td>
</tr>
<tr>
<td>Funding</td>
<td>25</td>
<td>Sources of funding and other support (such as supply of drugs), role of funders</td>
<td>Info submitted online</td>
</tr>
</tbody>
</table>
*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see [www.consort-statement.org](http://www.consort-statement.org).
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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