Medication-related interventions to improve medication safety and patient outcomes on transition from adult intensive care settings: a systematic review and meta-analysis

Richard S Bourne,1 Jennifer K Jennings,1 Maria Panagioti,2 Alexander Hodkinson,3 Anthea Sutton,4 Darren M Ashcroft3

ABSTRACT

Background Patients recovering from an episode in an intensive care unit (ICU) frequently experience medication errors on transition to the hospital ward. Structured handover recommendations often underestimate the challenges and complexity of ICU patient transitions. For adult ICU patients transitioning to a hospital ward, it is currently unclear what interventions reduce the risks of medication errors. The aims were to examine the impact of medication-related interventions on medication and patient outcomes on transition from adult ICU settings and identify barriers and facilitators to implementation.

Methods The systematic review protocol was preregistered on PROSPERO. Six electronic databases were searched until October 2020 for controlled and uncontrolled study designs that reported medication-related (ie, de-prescribing; medication errors) or patient-related outcomes (ie, mortality; length of stay). Risk of bias (RoB) assessment used V.2.0 and ROBINS-I Cochrane tools. Where feasible, random-effects meta-analysis was used for pooling the OR across studies. The quality of evidence was assessed by Grading of Recommendations, Assessment, Development and Evaluations.

Results Seventeen studies were eligible, 15 (88%) were uncontrolled before-after studies. The intervention components included education of staff (n=8 studies), medication review (n=7), guidelines (n=6), electronic transfer/handover tool or letter (n=4) and medicines reconciliation (n=4). Overall, pooled analysis of all interventions reduced risk of inappropriate medication continuation at ICU discharge (OR=0.45 (95% CI 0.31 to 0.63), I²=55%, n=9) and hospital discharge (OR=0.39 (95% CI 0.2 to 0.76), I²=75%, n=9). Multicomponent interventions, based on education of staff and guidelines, demonstrated no significant difference in inappropriate medication continuation at the ICU discharge point (OR 0.5 (95% CI 0.22 to 1.11), I²=62%, n=4), but were very effective in increasing de-prescribing outcomes on hospital discharge (OR 0.26 (95% CI 0.13 to 0.55), I²=67%, n=6). Facilitators to intervention delivery included ICU clinical pharmacist availability and participation in multiprofessional ward rounds, while barriers included increased workload associated with the discharge intervention process.

Conclusions Multicomponent interventions based on education of staff and guidelines were effective at achieving almost four times more de-prescribing of inappropriate medication by the time of patient hospital discharge. Based on the findings, practice and policy recommendations are made and guidance is provided on the need for, and design of theory informed interventions in this area, including the requirement for process and economic evaluations.

BACKGROUND

Delivering quality and safety at patient care transitions is challenging and complex,1,2 with patient outcomes affected by a wide range of interacting system and process components.2 Medication safety in transitions of patient care is a key priority area for the third WHO’s Global Patient Safety Challenge—‘medication without harm’.3,4

For adult patients surviving an intensive care unit (ICU) care episode, the transition to a hospital ward is especially challenging for care continuity and safety.5–6 ICU patients may experience a protracted recovery, further compounded by polypharmacy and care fragmentation.7 They also encounter frequent medication changes, with many chronic medicines discontinued and acute medication commenced,8–10 presenting a patient safety concern,11 particularly at the point of transition.12

Medication errors (MEs) are common in adult ICU patients at the interface of transfer to the hospital ward, with MEs reported to occur in between 46% and 74% of patients.13–15 The most commonly reported types of ME involve continuation of potentially inappropriate
medication, discontinuation of important chronic medication and inappropriate dose or route of administration.\textsuperscript{13–15} The reported incidence of adverse drug events (ADEs) related to ICU patient transfer varies from 6% to 70%,\textsuperscript{13,15,16} according to surveillance period and methodology employed, being highest in the intervention study with prospectively collected data.\textsuperscript{13} MEs post-ICU care can also continue long after patient hospital discharge.\textsuperscript{17–20} Pre-existing polypharmacy burden may predict ME risk,\textsuperscript{21} and the risk of unplanned hospital readmission.\textsuperscript{22}

To mitigate this increased patient safety risk, the European Society of Intensive Care Medicine recommends use of a standardised handover procedure, including an explanation of medication changes and treatment plans, on patient transfer from ICU.\textsuperscript{23} However, ICU medication-related discharge practices remain inconsistent.\textsuperscript{24–27} Contributors to variation in practice include uncertainty over key intervention components and processes,\textsuperscript{24} availability of important medicines optimisation resources,\textsuperscript{25} and staff communication failures\textsuperscript{26} in the context of an important care interface.\textsuperscript{6} Moreover, in isolation, the recommended handover procedure does not adequately address the challenges and complexity of patient care transitions including the importance of patient and family engagement, medicines reconciliation and medication review.\textsuperscript{1,2,4,6,28}

A recent systematic review demonstrated the benefits of pharmacy-led interventions to improve de-prescribing of stress ulceration prophylaxis (SUP) at ICU and hospital discharge points.\textsuperscript{29} However, a broader scope and multiprofessional approach is required to meet the wider medicines optimisation and communication challenges to transitional medication continuity and safety.\textsuperscript{4} For ICU patient to hospital ward transitions, it is unclear what medication-related intervention components are required and their efficacy, timing and mode of delivery. This information is required to help optimise existing medicines-related practice for ICU patients on transition to a hospital ward, and aid identification of evidence gaps, informing the need and design of further research to improve patient safety.

This systematic review and meta-analysis aimed to (i) examine the impact of medication-related interventions on medication and patient outcomes on transition from adult ICU settings and (ii) identify barriers and facilitators during intervention implementation.

\textbf{METHODS}

We performed a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.\textsuperscript{30} The protocol was preregistered on the international prospective register of systematic reviews (PROSPERO) database (CRD42020210638). Patient and public involvement and engagement was provided by representatives from intensive care and emergency care forums in the scope of review and planned dissemination of results.

\textbf{Eligibility criteria}

We included studies conducted in adult (≥18 years old) ICU patients surviving to transition to a hospital ward, investigating any medication-related interventions designed to affect medication continuity, safety or efficacy for ICU patients transitioning to a hospital ward, compared with usual care; that is, a non-exposed control group or historical group in a before-after study, evaluating medication-related (eg, MEs) or patient-related outcomes (eg, length of stay, mortality). Interventions had to be conducted before or within 48 hours of ICU patient transition to the hospital ward. We used the Cochrane Effective Practice and Organisation of Care Group criteria as a guide for study eligibility.\textsuperscript{31} Randomised controlled trials (RCTs) and non-randomised controlled and uncontrolled trials (including ‘before-after’ and ‘interrupted time series’ designs) were eligible for inclusion. Review articles, studies based on simulation and conference abstracts were excluded.

\textbf{Information sources}

In October 2020, the following databases were searched from inception without language restrictions: MEDLINE and MEDLINE Epub Ahead of Print, In-Process and Other Non-Indexed Citations and Daily; EMBASE; CINAHL; International Pharmaceutical Abstracts; The Cochrane Library; Science Citation Index. A search of the trial registries International Clinical Trials Registry Platform and ClinicalTrials.gov was conducted in August 2021 (online supplemental file 1).

\textbf{Selection process}

Two independent reviewers (RSB, JKJ) participated in each phase of the selection process. Any disagreement between reviewers was resolved by discussion, with arbitration by a third reviewer (DMA) when required. First, titles and abstracts were screened based on our eligibility criteria. Second, full texts were screened. Finally, reference lists of included studies and any relevant reviews were checked for any further relevant references. The citation search facility in Web of Science was used to identify any relevant cited references and additional studies by key authors. Authors of all eligible abstracts published within the last 2 years were contacted to confirm recent or planned publication.\textsuperscript{32–36}

\textbf{Data extraction}

Two reviewers (RSB, JKJ) independently extracted data in duplicate from included studies using a standardised data extraction form (with cross-checking validation process). The structured data collection form
was prepiloted, and data inputted into a proprietary software database (Covidence; www.covidence.org).

Risk of bias in individual studies
Quality assessment of individual studies was done by two independent authors (RSB, JKJ) using the Cochrane risk of bias (RoB) V.2.0 tool for RCTs,35 and ROBINS-I for non-randomised studies.38 Any disagreement was resolved by discussion, with arbitration by a third independent reviewer (MP) when required. RoB judgements are presented using the robvis visualisation tool (www.riskofbias.info/welcome/robvis-visualization-tool). Studies with a ‘high’ or ‘critical’ RoB assessment37 38 were excluded from any meta-analysis.

Confidence in overall evidence using Grading of Recommendations, Assessment, Development and Evaluations
We undertook a Grading of Recommendations, Assessment, Development and Evaluations (GRADE) assessment using the standard five GRADE criteria.39 We used ‘summary of findings’ tables to provide outcome-specific information related to the overall quality of evidence from studies included in comparisons, the magnitude of effect of the interventions examined and the sum of available data on the outcomes we considered.

Data synthesis
Data regarding medication-related interventions were summarised and described separately using the TIDieR framework.40 Barriers and facilitators in the primary research papers were summarised to allow comparison with those already identified.7

Meta-analysis was planned if comparable studies (design and outcome(s) reported) were identified. Before meta-analysis, we transformed data onto the uniform log odds scale using the Comprehensive Meta-Analysis (V.3) software (Biostat, New Jersey, USA). Then for all of the comparable ‘uncontrolled before-and-after studies’ with the relevant outcome data we meta-analysed using the DerSimonian-Laird random-effects model.41 The Hartung-Knapp random-effects method for pooling42 was used instead of DerSimonian-Laird, as it is a more robust method of choice when study sizes are small and there is considerable heterogeneity, as likely to be present in the non-randomised uncontrolled trials identified.

Statistical heterogeneity for assessment of comparability of studies was undertaken by visual inspection of forest plots and I² statistic (0%–25% low; 25%–74% substantial and ≥75% considerable heterogeneity) with the associated 95% CIs.43 For each meta-analysis with 10 studies or more, funnel plots, Begg’s and Egger’s test were used to examine potential publication bias. The trim-and-fill method was used as a sensitivity analysis to observe cases of small study publication bias.44 We planned subgroup analyses if sufficient data were available for studies with comparable interventions and outcome measures. All meta-analyses were performed in the statistical software R (V.4.0.3) with packages meta45 and metafor.46

RESULTS
Study inclusion
The literature searches identified 3153 references, after removal of duplicates, abstract and title screening and then assessment of full-text eligibility, 17 studies were included (table 1).13 14 47–61 The publications of Wohlt et al (before)62 and Hatch et al (after)59 were considered as a single study referenced as Hatch et al,59 for the purposes of this systematic review. The PRISMA flow chart for study inclusion is shown figure 1.

Characteristics of included studies
Most of the studies (76%) were from North America (n=12 the USA, n=1 Canada),47–53 55–60 three from Europe (n=2 The Netherlands, n=1 Belgium),13 14 61 and one from Australia54 (table 1). Only the study by Heselmans et al was an RCT, 15 were uncontrolled before-after studies13 47–49 51–61 and one was an uncontrolled interrupted time-series analyses.50 Most studies (n=14, 82%) were conducted in single centres, three were multicentre studies.13 14 54 Approximately one-third of the studies (n=6, 35%) were prospective in data collection and evaluation.13 14 50 54 56 61 Interventions are fully described according to the TIDieR framework (online supplemental table S1).40

Characteristics of interventions
Intervention components
Nine (53%) of the studies examined a single intervention component (table 1 and online supplemental table S1).44 47–50 52 55 56 61 The key intervention components described were education of staff, medication review, guidelines, electronic transfer/hand-over checklist or letter and medicines reconciliation. Multicomponent interventions,51 53 54 57–59 targeted inappropriate medication continuation at transfer points. These were based on education of staff and guidelines, with three studies also including a medication review element.51 53 54

Education of staff
Education of staff was an intervention component in eight studies (47%).47 51 53 54 57–60 Studies varied by healthcare professionals the education was targeted at. Uniprofessional,47 53 54 58 60 educational approaches were more commonly employed than multiprofessional.51 57 59 Mode of and frequency of delivery varied across the studies (table 1 and online supplemental table S1).
### Table 1 Summary of study characteristics

<table>
<thead>
<tr>
<th>Study/Country</th>
<th>Study design/centres (number)</th>
<th>Intervention target</th>
<th>Participants</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Participant numbers (control/before: intervention/after)</th>
<th>Intervention description, (components) and (timing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anstey et al</td>
<td>Before-after (B-A); prospective; multi (n=5)</td>
<td>De-escalation of inappropriate stress ulcer prophylaxis (SUP)</td>
<td>Adult intensive care unit (ICU) patients (medical, surgical, cardiothoracic)</td>
<td>Inclusion: consecutive ICU patients admitted during the active study period&lt;br&gt;Exclusion: patients &lt; 18 years of age</td>
<td></td>
<td>842 (469: 373)</td>
<td>SUP de-escalation bundle (education of ICU medical staff; guidelines; pharmacist-lead prescription discontinuation) (ICU stay)</td>
</tr>
<tr>
<td>Bosma et al</td>
<td>B-A; prospective; multi (n=2)</td>
<td>Medication errors (MEs) on ICU discharge</td>
<td>Adult ICU patients (medical, surgical, neurosurgery, cardiology)</td>
<td>Inclusion: patients admitted ≥ 1 regular medicine with ICU stay &gt; 24 hours. Discharge (disch) patients included if in admission (adm) study part, surviving ≥ 24 hours after ICU disch&lt;br&gt;Exclusion: patients transferred to another hospital, adm and disch same weekend period, patients unable to understand Dutch or English</td>
<td></td>
<td>380 (203: 177)</td>
<td>Medication reviews (med rev) at care transitions (by ICU pharmacist; in patient rounds; combined with medication review (med rev) by pharmacist with ICU medical staff review to create ICU disch medication list. Medication advice included as supplement to the ward discharge letter. Discharge medication prepopulated on the ward electronic (e-) prescribing system (ICU adm, ICU stay, ICU disch)</td>
</tr>
<tr>
<td>Buckley et al</td>
<td>B-A; retrospective; single</td>
<td>De-escalation of inappropriate SUP</td>
<td>Adult ICU patients ≥ 18 years</td>
<td>Inclusion: all patients receiving acid suppressing therapy (AST)</td>
<td>Exclusion: patients on treatment for gastrointestinal (GI) disorders or admitted on AST. Patients in the emergency department, rehabilitation or psychiatric wards</td>
<td>341 (174: 167)</td>
<td>SUP de-escalation programme (pharmacist-led authorised stress ulceration prescription management) (ICU stay, ward stay)</td>
</tr>
<tr>
<td>Coon et al</td>
<td>B-A; prospective; single</td>
<td>Med rec (of specific intravenous vasoactives)</td>
<td>Adult ICU patients (neurosurgery)</td>
<td>Inclusion: all consecutive ICU patients transferred to the ward</td>
<td></td>
<td>261 (130: 131)</td>
<td>Structured ICU handover checklist (incorporated into e-discharge documentation (by ICU medical staff)) (ICU disch)</td>
</tr>
<tr>
<td>D’Angelo et al</td>
<td>B-A; retrospective; single</td>
<td>De-escalation of inappropriate antipsychotics</td>
<td>Adult ICU patients (medical)</td>
<td>Inclusion: all ICU patients initiated on antipsychotic therapy for ICU delirium ≥ 24 hours prior to ward transfer</td>
<td></td>
<td>281 (140: 141)</td>
<td>Antipsychotic discontinuation bundle (education of medical, nursing and pharmacy staff; clinical guidelines (including non-pharmacological interventions and de-escalation based on delirium screening) (ICU stay)</td>
</tr>
<tr>
<td>Hammond et al</td>
<td>B-A; retrospective; single</td>
<td>De-escalation of inappropriate SUP</td>
<td>Adult ICU patients (medical) ≥ 18 years</td>
<td>Inclusion: all patients prescribed AST&lt;br&gt;Exclusion: diagnosis of GI bleed, receiving AST on ICU adm, or history of Zöllinger-Ellison syndrome</td>
<td></td>
<td>219 (101: 118)</td>
<td>Educational interventions for SUP (education of ICU medical staff; guideline; pharmacist on ward rounds to support education) (ICU stay)</td>
</tr>
<tr>
<td>(B) Wohlt et al</td>
<td>B-A; retrospective; single</td>
<td>De-escalation of inappropriate SUP</td>
<td>Adult ICU patients (medical, surgical) ≥ 18 years</td>
<td>Inclusion: all ICU patients&lt;br&gt;Exclusion: patients with a GI bleed, Zöllinger-Ellison syndrome, prisoner status or died in hospital</td>
<td></td>
<td>750 (394: 356)</td>
<td>Education on SUP (education of ICU and ward medical and pharmacy staff; audit and feedback of preintervention results; guideline) (ICU stay, ward stay)</td>
</tr>
<tr>
<td>Heselmans et al</td>
<td>Randomised controlled trial; prospective; multi (n=3)</td>
<td>Drug-related problems in patients after ICU to ward transfer</td>
<td>ICU patients (medical, surgical) ≥ 15 years</td>
<td>Inclusion: patients with ICU stay ≥ 3 days and transferred to surgical, medical or geriatric ward&lt;br&gt;Exclusion: patients with a ‘do not resuscitate’ order</td>
<td></td>
<td>600 (299: 301)</td>
<td>Medication review by ward-based pharmacists after ICU patient transfer (ward stay &lt; 48 hours of ICU transfer)</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Study/Country</th>
<th>Study design/centres (number)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Kram et al USA</td>
<td>B-A; retrospective; single</td>
<td>De-escalation of inappropriate antipsychotics</td>
<td>Adult ICU patients (medical, surgical, cardiothoracic, neurosciences and cardiac ≥18 years</td>
<td>358 (133: 225)</td>
<td>E-handover tool (prompting medication review by pharmacists (ICU and ward); supported by education (pharmacy staff), including audit and feedback of preintervention results) (ICU stay; ICU discharge; ward stay)</td>
</tr>
<tr>
<td>Medlock et al</td>
<td>B-A; prospective; single</td>
<td>ICU e-discharge letter (template included medical details)</td>
<td>Adult ICU patients (medical, surgical) Inclusion: all critical care patients (discharged alive or dead)</td>
<td>6823 (1872: 4951)</td>
<td>E-letter to ward medical staff and general practitioner (with template and automatic assignment to ICU medical staff) (ICU discharge)</td>
</tr>
<tr>
<td>Meena et al USA</td>
<td>B-A; retrospective; single</td>
<td>De-escalation of inappropriate SUP</td>
<td>Adult ICU patients Inclusion: all ICU patients Exclusion: patients already taking SUP on admission, therapeutic indication for SUP, patients died within 24 hours of admission</td>
<td>224 (106: 118)</td>
<td>Education sessions for medical staff (didactic education session for junior medical staff) (ICU stay)</td>
</tr>
<tr>
<td>Parsons Leigh et al</td>
<td>B-A; retrospective; single</td>
<td>ICU e-transfer tool with eight key elements (including active medicines and med rec)</td>
<td>Adult ICU patients (medical, surgical, neurosurgical and trauma) Inclusion: randomly selected cohort of ICU patients transferred to an inpatient ward Exclusion: ICU patients not transferred to an inpatient ward</td>
<td>60 (30: 30)</td>
<td>E-transfer tool (auto-population of elements, eg, medicines to continue on ward transfer with facility to review and refine; facility to compare with preadmission med rec and identify changes (by medical staff)) (ICU discharge)</td>
</tr>
<tr>
<td>Pavlov et al USA</td>
<td>B-A; retrospective; single</td>
<td>De-escalation of inappropriate SUP and bronchodilators</td>
<td>Adult ICU patients (medical, surgical) Inclusion: ICU patients on acid blockers or bronchodilators Exclusion: patients who died during their adm or still in ICU on study data extraction</td>
<td>454 (201: 253)</td>
<td>Med rec (on hospital adm (pharmacy technician) and ICU discharge (ICU nurse), with medical staff confirmation and in reconciliation with medication on ICU discharge) (ICU discharge)</td>
</tr>
<tr>
<td>Pronovost et al</td>
<td>Time-series analysis; prospective; single</td>
<td>MEs on ICU discharge</td>
<td>Adult ICU patients (surgical) Inclusion: random selection of 10–15 patients per week</td>
<td>No information</td>
<td>Med rec by ICU nurses on patient adm and ICU discharge. Specific MEs prompted discussion with ICU medical staff (ICU adm, ICU discharge)</td>
</tr>
<tr>
<td>Stuart et al USA</td>
<td>B-A; retrospective; single</td>
<td>De-escalation of inappropriate antipsychotics</td>
<td>Adult ICU patients (medical, surgical, cardiac) Inclusion: ICU patients with antipsychotic prescribed for delirium Exclusion: palliative care or died, on antipsychotics pre-ICU adm, or non-delirium psychiatric indication</td>
<td>158 (79: 79)</td>
<td>Pharmacist-led de-escalation protocol (de-escalation guideline with education of staff (ICU and ward pharmacists). Pharmacists authorised to discontinue or taper antipsychotics in ICU patients with resolved delirium symptoms) (ICU stay (direct patient discharge), ward stay)</td>
</tr>
<tr>
<td>Tasaka et al USA</td>
<td>B-A; retrospective; single</td>
<td>De-escalation of inappropriate SUP</td>
<td>Adult ICU patients (medical, surgical) Inclusion: all ICU patients Exclusion: patients requiring continued AST (eg, active GI bleed), or no indication for AST (eg, total gastrectomy)</td>
<td>124 (74: 50)</td>
<td>SUP de-escalation bundle. Guideline education of staff (medical, nurses, pharmacists, dietitians), multifaceted awareness campaign, pharmacist SUP recommendations (on care rounds, or by text/telephone) with documentation in e-medical notes. SUP not included in the e-prescribing core or ICU adm order sets (ICU stay)</td>
</tr>
</tbody>
</table>

Table 1 Continued
Seven studies included a specific medication review component within the intervention\textsuperscript{13 14 51 53–55 60} (table 1 and online supplemental table S1). Five of these studies included a pharmacist-led medication review as part of a multicomponent intervention targeted at a specific de-prescribing initiative, either of inappropriate SUP\textsuperscript{51 54 55} or use of antipsychotics.\textsuperscript{53 60}

**Guidelines**

Six studies (35\%) implemented a clinical guideline intervention component,\textsuperscript{51 53 54 57–59} four focused on de-escalation of inappropriate medication on transfer\textsuperscript{51 53 54 57} (table 1 and online supplemental table S1). Three studies had clear multiprofessional participation in the guideline development.\textsuperscript{51 57 59} Implementation of the clinical guidelines included education and awareness of staff in all studies.\textsuperscript{51 53 54 57–59}

**Medicines reconciliation**

Four studies investigated a medicines reconciliation intervention (table 1 and online supplemental table S1).\textsuperscript{13 49 50 52} The healthcare professionals undertaking the medication review varied, with pharmacist,\textsuperscript{13} pharmacy technician,\textsuperscript{49} ICU nurse,\textsuperscript{50} and ICU nurse with a pharmacist involved.\textsuperscript{52} All medicines reconciliation processes required review and authorisation by medical staff, with pharmacist medication review and advice also provided in the study by Bosma \textit{et al}.\textsuperscript{13} Medicines reconciliation was undertaken on patient ICU admission and ICU discharge in all four studies.\textsuperscript{13 49 50 52} Bosma \textit{et al}\textsuperscript{13} provided detailed information on the delivery and quality of medicines reconciliation on the interfaces of care.

**Electronic transfer/handover tool or letter**

Four studies\textsuperscript{48 56 60 61} implemented an intervention designed to improve communication from the ICU to the hospital ward and included a medication-related component (table 1 and online supplemental table S1). The communication was directed at a range of healthcare professionals: general practitioners,\textsuperscript{61} ICU and hospital ward pharmacists,\textsuperscript{60} and hospital ward medical staff.\textsuperscript{48 56}

**Intervention timing**

There was a high degree of variation with regard to the timing of the intervention components delivered in the patient acute care pathway (table 1 and online supplemental table S1). Most (n=10, 59\%) of studies investigated an intervention delivered at a single time-point in the patient pathway.\textsuperscript{54 47–49 51 54 56–58 61} For five of these studies, this was during the ICU patient stay.\textsuperscript{47 51 54 57 58} which was also the period most interventions included (n=10, 59\%).\textsuperscript{13 47 51 53–55 57–60} Eight studies (47\%) also included the ICU discharge period in the intervention delivery.\textsuperscript{13 48–50 52 56 60 61}
Five studies included an intervention element that included the patient’s hospital ward stay, three of which included a medication review intervention component.

Facilitators and barriers to intervention delivery
Most studies (12, 71%) identified facilitators to the intervention delivery (table 2). The availability of specialist ICU clinical pharmacists contributing to a range of activities including multi-professional ward rounds, staff education, medicines reconciliation, medication reviews and de-prescribing were highlighted in seven studies. Integration of the electronic transfer/handover tool or letter into existing electronic systems was reported as a facilitator in three studies, as was auto-population of data on transfer reports, and software tailoring. The important role of a supportive quality improvement organisational culture was emphasised in two studies.

Fewer studies (n=7, 41%) provided an indication of intervention barriers (table 2). The most common barrier cited (n=3, 18%) was increased workload associated with the intervention. Multi-professional collaboration was reported as barrier to intervention delivery when limited, and a facilitator when effective.

Outcomes
Medication outcomes
We describe the medication outcomes according to the focus of the intervention on those outcomes.

There was sufficient de-prescribing medication outcome data from intervention studies to conduct a meta-analysis. A narrative synthesis of other medication outcome data and findings related to interventions...
with medicines optimisation, patient and economic evaluation outcomes are presented. Most studies used medical notes review for medication outcomes. A summary of the study outcomes and measures is shown online supplemental table S2.

**De-prescribing outcomes**

Eleven studies (65%) focused on de-escalation of inappropriate medication therapy on ICU discharge or at hospital discharge (table 1),47 49 51–55 57–60 the most common focus being the reduction of inappropriate SUP.47 51 52 54 55 58 59

**Medicines optimisation outcomes**

Interventions targeted on medicines optimisation outcomes had a much broader remit, examining the clinical effectiveness and safety of all the patient’s medicines, usually employing a combination of medicines reconciliation and medication review.63 Heselmans et al14 focused on a medication review intervention conducted in three Belgian hospitals by hospital pharmacists on the ward within 48 hours of the ICU patient transfer; 54.1% (203/375) of the drug-related problems (DRPs) were adjusted on time in the intervention group compared with 12.8% (47/368) in the control group. Compared with the control group, the odds of implementing a change in medication therapy recommendations in the intervention group were 10-fold higher (OR 10.1, 95% CI 6.3 to 16.1), increasing to OR 15.6 (95% CI 9.4 to 25.9), when between-group differences in types of DRPs were accounted for.

In a two-centre before-after study, Bosma et al13 investigated the effect of a medicines reconciliation intervention on discharge medication transfer errors (any unintentional discrepancy between the patient’s prescription chart and best possible ward medication list at 24 hours after discharge) (online supplemental table S2). On ICU discharge, 41.2% (73/177) of patients in the intervention period had at least one ME compared with 73.9% (150/203) of patients in the before phase. After correcting for baseline differences in patient severity of illness, patients in the intervention period had an adjusted OR 0.24 (95% CI 0.15 to 0.37) for a discharge ME.

**Documentation and communication outcomes**

Electronic transfer/handover tool or letters improved the timeliness of information transfer and completeness of information provision.48 61

### Table 2 Facilitators and barriers identified from the selected studies classified by system factors

<table>
<thead>
<tr>
<th>System factor</th>
<th>Facilitator/Barrier</th>
<th>Studies, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare professionals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical pharmacist availability</td>
<td>Facilitator</td>
<td>7 (41%)31 51 53-55 58 59</td>
</tr>
<tr>
<td>Multiprofessional collaboration</td>
<td>Both (facilitator when good collaboration, barrier when poor collaboration)</td>
<td>3 (18%)14 50 51</td>
</tr>
<tr>
<td>Staff perception of limited intervention value</td>
<td>Barrier</td>
<td>2 (12%)32 56</td>
</tr>
<tr>
<td>Off shift hours (eg, clinical pharmacists)</td>
<td>Barrier</td>
<td>2 (12%)33</td>
</tr>
<tr>
<td>Tasks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacist participation on ICU multiprofessional ward round</td>
<td>Facilitator</td>
<td>4 (24%)31 51 58 59</td>
</tr>
<tr>
<td>Increased workload associated with discharge intervention process (eg, medicines reconciliation, checklist)</td>
<td>Barrier</td>
<td>3 (18%)31 50 56</td>
</tr>
<tr>
<td>Structured approach to medicines reconciliation</td>
<td>Facilitator</td>
<td>2 (12%)31 50</td>
</tr>
<tr>
<td>Gaps in educational process</td>
<td>Barrier</td>
<td>2 (12%)32 58</td>
</tr>
<tr>
<td>Education package revised, condensed and delivered regularly</td>
<td>Facilitator</td>
<td>1 (6%)31</td>
</tr>
<tr>
<td>Focus on the care transition</td>
<td>Facilitator</td>
<td>1 (6%)31</td>
</tr>
<tr>
<td>Technologies and tools</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auto-population of discharge information from electronic health record</td>
<td>Facilitator</td>
<td>3 (18%)48 50 61</td>
</tr>
<tr>
<td>Checklist integrated into existing workflow/systems</td>
<td>Facilitator</td>
<td>3 (18%)48 56 61</td>
</tr>
<tr>
<td>Tailored discharge letter/tool software</td>
<td>Facilitator</td>
<td>3 (18%)48 60 61</td>
</tr>
<tr>
<td>Guideline and supporting documentation</td>
<td>Facilitator</td>
<td>1 (6%)39</td>
</tr>
<tr>
<td>Organisational conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality improvement culture</td>
<td>Facilitator</td>
<td>2 (12%)40 61</td>
</tr>
<tr>
<td>Task allocation</td>
<td>Both</td>
<td>2 (12%)40 61</td>
</tr>
<tr>
<td>Ability to initiate the summary on patient admission and edit throughout the ICU stay</td>
<td>Facilitator</td>
<td>1 (6%)38</td>
</tr>
<tr>
<td>Patient discharged from ICU out of hours</td>
<td>Barrier</td>
<td>1 (6%)38</td>
</tr>
<tr>
<td>Short discharge time-frame</td>
<td>Barrier</td>
<td>1 (6%)38</td>
</tr>
</tbody>
</table>

ICU, intensive care unit.
Systematic review

Patient outcomes

Eight studies (47%) reported between-group comparison of patient outcomes (online supplemental table S2).13 14 49 53 56 60 61 No mortality difference was reported in the medication review RCT,14 or in one communication before-after intervention study.61 Two studies included an assessment of actual,13 or potential ADEs,13 with a significant reduction in the latter.13 The RCT investigating medication reviews, reported no differences between the intervention and control groups in any patient outcomes (mortality rate, ICU readmission rate or hospital length of stay).14 Three other studies reported no effect of the intervention on hospital length of stay.53 56 60

Risk of bias and overall quality of evidence

Overall, the quality of the studies was low (online supplemental figures S1 and S2). All the non-randomised studies were assessed as moderate to serious RoB except one,50 which was graded as critical RoB and was excluded from the meta-analysis. The RCT by Heselmans et al14 was also assessed as high RoB due to the randomisation process domain. The GRADE assessments for the overall quality of evidence for the main meta-analysis and subgroup analysis of studies focused on the de-escalation of inappropriate medication on ICU and hospital discharge are shown (online supplemental table S3).

Main meta-analysis

The meta-analysis was undertaken for interventions that had the common outcome of de-escalation of inappropriate medication (de-prescribing) at ICU and hospital discharge points (figure 2). Compared with the before period of usual care, pooled analysis of all interventions reduced the risk of inappropriate medication continuation at ICU discharge (OR=0.45 (95% CI 0.31 to 0.63), I²=55 (5–79) %, n=9 studies) and hospital discharge (OR=0.39 (95% CI 0.2 to 0.76), I²=75 (52–87) %, n=9 studies). There was no evidence of publication bias as indicated by funnel plot symmetry, and the non-significant Egger’s regression test (p=0.583) and trim-and-fill method (p=0.152) for the primary outcome (online supplemental figure S3). The quality of evidence for ICU discharge and hospital discharge points were considered low to very low, respectively (online supplemental table S3).

Subgroup analysis

Subgroup meta-analysis showed that multicomponent interventions (based on education of staff and guidelines) led to a reduction in inappropriate medication continuation at the hospital discharge point (OR=0.26 (95% CI 0.13 to 0.55), I²=67 (21–86) %, n=6 studies). There was an indication of benefit at ICU discharge, but this did not reach statistical significance (OR=0.5 (95% CI 0.22 to 1.11), I²=62 (0–87) %, n=4 studies) (figure 3). Quality of evidence was moderate at hospital discharge and low for the ICU transition point (online supplemental table S3). In contrast, single component interventions (education of staff, medicines reconciliation, medication review) demonstrated a reduction in inappropriate medication continuation at ICU discharge (OR=0.42 (95% CI 0.24 to 0.74), I²=60 (0–85) %, n=5 studies), but not hospital discharge (OR=0.77 (95% CI 0.16 to 3.74), I²=50 (0–86) %, n=3 studies) (education of staff, medicines reconciliation, electronic handover tool) (figure 3); quality of evidence was graded low and very low, respectively (online supplemental table S3). No
further subgroup analyses of medication review and medicines reconciliation interventions were undertaken given the small number of studies involving high levels of heterogeneity and imprecise data.

**DISCUSSION**

**Summary of main findings**

This systematic review has found that pooled analysis of specific interventions (education of staff, medication review, guidelines, medicines reconciliation, electronic handover tool) to reduce inappropriate medication continuation on ICU and hospital discharge were effective, with more than twice the likelihood of effective de-prescribing (low and very low quality of evidence). Multicomponent interventions based on education of staff and guidelines were associated with an almost fourfold higher rate of inappropriate medication discontinuation at hospital discharge compared with usual care, with moderate quality of evidence. Single component interventions (education of staff, medicines reconciliation, medication review) were twice as likely as usual care to reduce inappropriate medication continuation at ICU discharge only (shown by low quality of evidence).

Patient and economic evaluation outcomes were reported in a minority of studies. Only one study demonstrated a reduction in potential ADEs with an ICU medicines reconciliation intervention, also providing the most compelling health economic data. Structured electronic transfer/handover tool or letters both within ICU, and beyond ICU to the hospital ward and general practitioners, improved medication-related completeness and communication.

Successful delivery of complex interventions usually requires a combination of several factors including resources, education and training of staff. Medication review by hospital ward-based clinical pharmacists soon after ICU patient transfer was very effective in the reduction of clinically important DRPs, also providing the most compelling health economic data. Structured electronic transfer/handover tool or letters both within ICU, and beyond ICU to the hospital ward and general practitioners, improved medication-related completeness and communication.

The identified facilitators and barriers to medication-related interventions are consistent with, and add further specific detail to, those already identified in other wider reviews of interventions to improve ICU patient continuity of care. These facilitators and barriers should inform the development and implementation of medication outcome interventions, particularly when staff behaviour change across different professions and teams is required.

**Comparison with previous research**

The main meta-analysis results are consistent with a recent systematic review of pharmacy-supported interventions to reduce inappropriate continuation of SUP in patients after ICU and hospital discharge that reported similar effectiveness. However, our meta-analyses considered discontinuation of all potentially inappropriate medication and were unconstrained by interventions delivered by a single profession. Multicomponent de-prescribing interventions primarily consisted of policy-type (guidelines) and single intervention functions (education (and training) of staff), sometimes supported by audit and feedback, to affect staff behaviour change and likely intervention adoption. This combination re-enforces information and desired practice, which have been reported to be effective in changing healthcare staff behaviours in de-prescribing interventions.

A recent systemic review of medication-related interventions delivered in hospital and following discharge reported that the size of the treatment effect increased with the intensity (factoring number and repetition of components) of medication-related intervention delivered. However, such intervention intensity needs to be balanced with routine deliverability.

**Strengths and limitations**

This systematic review had several strengths including multidisciplinary team expertise, comprehensive searches, detailed critical appraisal of the studies and presentation of different study elements. However,
there are also limitations. The conclusions are limited by the availability of study designs (uncontrolled before-after) employed, with inherent RoB that was mainly due to baseline confounding risks. We did not have sufficient studies to undertake a sensitivity analysis to examine the impact of the RoB assessment, although since the vast majority of studies were high risk, a sensitivity analysis is very unlikely to show any different findings. The meta-analysis was limited to a subgroup outcome of medicines optimisation, that is, de-prescribing of SUP, antipsychotics and bronchodilators. Wider de-prescribing foci are required, for example, opioid analgesia, to address the risk of inappropriate long-term continuation. Although studies used similar definitions for the respective outcomes of multiple inappropriate medications, as well as use of patient chart reviews, there are still significant inconsistencies in terms of design and exact methods. We were unable to describe the intervention mechanisms of action as most studies neglected to provide process evaluation elements.

Implications for policy and practice
Intervention to reduce medication-related harm for patients on transitions of care is a policy and practice priority, being particularly pertinent to the complexity of acutely ill patient care transition to a hospital ward. Our findings suggest that multicomponent interventions, including education of staff and guidelines, are promising in reducing inappropriate continuation of acute medication by hospital discharge (moderate quality of evidence). It seems reasonable to consider routine adoption of these low-risk and likely low-cost interventions. However, further research is required on how best to improve the more challenging medicines optimisation aspect, re-introduction of clinically important chronic medication, for ICU patients transferring to the ward and beyond. To inform this research, consensus on the key medication-related interventions to use and what medication and patient outcomes measures to test these against, as well as how the human factors involved in medication transfer errors can be addressed are required. The resulting intervention is likely to be a theory-informed multi-component intervention that should be evaluated in a multicentre cluster or stepped-wedge RCT that includes a health economic evaluation. Process evaluation capable of informing the complex intervention mechanism of action and theory is also needed. In turn, this would support the implementation and delivery of practice and future policy recommendations.

CONCLUSIONS
This systematic review and meta-analysis newly identified that interventions aimed at reducing inappropriate medication continuation on patient ICU discharge and hospital discharge increased de-prescribing efficacy. Multicomponent interventions, built on education of staff and guidelines, appeared most effective in reducing inappropriate medication by hospital discharge. However, none of the de-prescribing initiatives exhibited beneficial effects on patient outcomes. More complex interventions such as medication review and medicines reconciliation, targeted at reducing MEs and medication-related problems on ICU discharge, were very effective and reduced potential ADEs. Our findings highlight the need to improve the quality and design of future prospective randomised intervention studies in this area.

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4National Institute for Health Research (NIHR) School for Primary Care Research, Division of Population Health, Health Services Research and Primary Care, School of Health Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK
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Contributors RSB was responsible for the conception of this systematic review. RSB, DMA and MP contributed to study design and data interpretation. AS and RSB designed the search strategy. RSB and JKJ were responsible for writing the manuscript. RSB and JKJ performed data acquisition, analysis and interpretation of the findings. AH conducted the statistical data analysis and interpretation of the results. All authors contributed to, read and approved the final manuscript. RSB is the guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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REFERENCES

620

33 Record J, Ozkinis T, Weaver ECC. Goals of care information rarely documented for critically ill patients even after a brief educational intervention. Journal of General Internal Medicine 2018;S704–5.


Additional File 1. Search strategy

A systematic search strategy was developed on MEDLINE by the information specialist (EEE) in consultation with the lead reviewer (AAA), to identify literature on medication-related interventions in the population of intensive care patients on transition to a hospital ward. The pilot search strategy was run on MEDLINE and the results shared with the lead reviewer to check that known studies were retrieved by the search. One known study was not retrieved, so additional search terms were added to improve the sensitivity of the search. The final search strategy was circulated to the review team for comment and no further changes were required.

The search strategy used a combination of free-text and thesaurus searching (where available). All databases were searched from inception to present, and no search limits were applied. The searches were run in October 2020 on the following sources:

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to October 09, 2020
- International Pharmaceutical Abstracts (via Ovid)
- Embase 1974 to 2020 October 13
- CINAHL via EBSCO (1981-present)
- Cochrane Database of Systematic Reviews Issue 10 of 12, October 2020
- Cochrane Central Register of Controlled Trials Issue 10 of 12, October 2020
- Science Citation Index Expanded (SCI-EXPANDED) –1900-present (via Web of Science)

Complete search strategies are provided below.

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<th>Database</th>
<th>Date Searched</th>
<th>Number of References Retrieved (including duplicates)</th>
</tr>
</thead>
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<tr>
<td>CINAHL via EBSCO</td>
<td>15/10/20</td>
<td>343</td>
</tr>
<tr>
<td>Cochrane Database of Systematic Reviews Issue 10 of 12, October 2020</td>
<td>15/10/20</td>
<td>60</td>
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</table>
Search Strategies

MEDLINE

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to October 09, 2020>

Search Strategy:

1. exp PATIENT DISCHARGE/ (30323)
2. exp Patient Transfer/ (8558)
3. (discharg* or transition* or transfer*).ti,ab. (1361480)
4. exp "Continuity of Patient Care"/ (247491)
5. or/1-4 (1566670)
6. exp MEDICATION RECONCILIATION/ (1167)
7. exp Inappropriate Prescribing/ (3395)
8. exp Medication Errors/ (17485)
9. exp Medication Systems/ (5510)
10. exp Medication Therapy Management/ (2192)
11. exp Drug Utilization/ (25613)
12. exp Potentially Inappropriate Medication List/ (507)
13. exp Pharmaceutical Preparations/ and (exp "Process Assessment (Health Care)"/ or exp "Continuity of Patient Care") (1474)
14  ((medication* or medicine* or drug* or prescribing or prescription*) adj1 (review* or reconciliation or optimisation or system* or error* or discrepancy or safety)).ti,ab. (26424)
15  ((medication* or medicine* or drug* prescribing or prescription*) and (adverse adj1 event*)).ti,ab. (22086)
16  ((medication* or medicine* or drug* or prescribing or prescription*) adj3 intervention*).ti,ab. (13076)
17  (communication adj5 (tool* or intervention* or system*)).ti,ab. (20641)
18  or/6-17 (120182)
19  5 and 18 (10151)
20  exp Critical Care/ (58522)
21  exp Intensive Care Units/ (85997)
22  exp Critical Illness/ (29697)
23  (ITU or ICU or ICUs or intensive care or critical care).ti,ab. (200296)
24  or/20-23 (258059)
25  19 and 24 (546)

---------------------
IPA

Ovid Technologies, Inc. Email Service

---------------------
Undertaken 13th October 2020
Search for: 1 and 4 and 10

Results: 189

Database: International Pharmaceutical Abstracts <1970 to September 2020>
Search Strategy:

1  (Intensive care or critical care or critical care unit$ or intensive care unit$ or critically ill or critical illness or ITU$ or ICU$).af. (8706)
2  (PATIENT DISCHARGE or Patient Transfer or Continuity of Patient Care or patient transition).af. (184)
3  (discharg$ or transition$ or transfer$).af. (21460)
4  2 or 3 (21480)
5  (MEDICATION RECONCILIATION or Medicines reconciliation or Medication Errors or Inappropriate Prescribing or Medication Systems or Drug Utilization or Medication Review or
Potentially Inappropriate Medication).af. (19805)

6     (((medication$ or medicine$ or drug$ or prescribing or prescription$) adj1 (review$ or reconciliation or optim$ation or system$ or error$ or discrep$ or safety))).af. (18750)
7     (((medication$ or medicine$ or drug$ prescribing or prescription$) and (adverse adj1 event$))).af. (3694)
8     (((medication$ or medicine$ or drug$ or prescribing or prescription$) adj3 intervention$)).af. (10351)
9     (communication adj5 (tool$ or intervention$ or system$)).af. (1266)
10     5 or 6 or 7 or 8 or 9 (44262)
11     1 and 4 and 10 (189)

**Embase**

Database: Embase <1974 to 2020 October 13>

Search Strategy:

1     *[hospital discharge]/ (13169)
2     *[patient transport]/ (8305)
3     (discharg* or transition* or transfer*).ti,ab. (1583038)
4     *[patient care]/ (68899)
5     or/1-4 (1652960)
6     *[medication therapy management]/ (4369)
7     *[inappropriate prescribing]/ (1551)
8     *[medication error]/ (8374)
9     *[hospital organization]/ (6476)
10    *[drug utilization]/ (5938)
11    *[potentially inappropriate medication]/ (917)
12    *[drug]/ (24905)
13    *[health care quality]/ (73500)
14    4 or 13 (139835)
15    12 and 14 (149)
16    (((medication$ or medicine$ or drug$ or prescribing or prescription$) adj1 (review$ or reconciliation or optim$ation or system$ or error$ or discrep$ or safety))).ti,ab. (42305)
17    (((medication$ or medicine$ or drug$ prescribing or prescription$) and (adverse adj1 event$))).ti,ab. (38470)
18    (((medication$ or medicine$ or drug$ or prescribing or prescription$) adj3 intervention$)).ti,ab. (19390)
19    (communication adj5 (tool$ or intervention$ or system$)).ti,ab. (24704)
20    or/6-11 (26781)
21    or/15-20 (140206)
22    *[intensive care]/ (62895)
23    *[intensive care unit]/ (34671)
24    *[critical illness]/ (12110)
25    (ITU or ICU or ICUs or intensive care or critical care).ti,ab. (305297)
26    or/22-25 (333889)
27    5 and 21 and 26 (907)
28    limit 27 to (conference abstracts or embase) (807)
CINAHL

S28 S22 AND S27

S27 S23 OR S24 OR S25 OR S26

S26 T1 (ITU or ICU or ICUs or intensive care or critical care) OR AB (ITU or ICU or ICUs or intensive care or critical care)

S25 (MH "Critical Illness")

S24 (MH "Intensive Care Units+")

S23 (MH "Critical Care+")

S22 S5 AND S21

S21 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S16 OR S17 OR S18 OR S19 OR S20

T1 (communication N5 (tool* or intervention* or system*)) OR AB (communication N5 (tool* or intervention* or system*))

S20 T1 ((medication* or medicine* or drug* or prescribing or prescription*) N3 intervention*) OR AB ((medication* or medicine* or drug* or prescribing or prescription*) N3 intervention*)

S19 T1 ((medication* or medicine* or drug* prescribing or prescription*) and (adverse N1 event*)) OR AB ((medication* or medicine* or drug* prescribing or prescription*) and (adverse N1 event*))
TI ((medication* or medicine* or drug* or prescribing or prescription*) N1 (review* or reconciliation or optimization or system* or error* or discrepancy* or safety)) OR AB ((medication* or medicine* or drug* or prescribing or prescription*) N1 (review* or reconciliation or optimization or system* or error* or discrepancy* or safety))

S16  S12 AND S15

S15  S13 OR S14

S14  (MH "Continuity of Patient Care+")

S13  (MH "Process Assessment (Health Care)+")

S12  (MH "Drugs+")

S11  (MH "Drug Utilization+")

S10  (MH "Medication Management")

S9  (MH "Medication Systems")

S8  (MH "Medication Errors+")

S7  (MH "Inappropriate Prescribing")

S6  (MH "Medication Reconciliation")
S5  S1 OR S2 OR S3 OR S4

S4  (MH "Continuity of Patient Care+")

TI ( (discharg* or transition* or transfer*) )

S3  OR AB ( (discharg* or transition* or transfer*) )

S2  (MH "Transfer, Discharge")

S1  (MH "Patient Discharge")

Cochrane Library

#1 MeSH descriptor: [Patient Discharge] explode all trees
#2 MeSH descriptor: [Patient Transfer] explode all trees
#3 ((discharg* or transition* or transfer*)):ti,ab,kw (Word variations have been searched)
#4 MeSH descriptor: [Continuity of Patient Care] explode all trees
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Medication Reconciliation] explode all trees
#7 MeSH descriptor: [Inappropriate Prescribing] explode all trees
#8 MeSH descriptor: [Medication Errors] explode all trees
#9 MeSH descriptor: [Medication Systems] explode all trees
#10 MeSH descriptor: [Medication Therapy Management] explode all trees
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#13 MeSH descriptor: [Pharmaceutical Preparations] explode all trees
#14 MeSH descriptor: [Process Assessment, Health Care] explode all trees
#15 MeSH descriptor: [Continuity of Patient Care] explode all trees
#16 #14 or #15
#17 #13 and #16
#18 (((medication* or medicine* or drug* or prescribing or prescription*) NEAR/1 (review* or reconciliation or optim?ation or system* or error* or discrepancy* or safety))):ti,ab,kw (Word variations have been searched)
#19 (((medication* or medicine* or drug* prescribing or prescription*) and (adverse NEAR/1 event*)):ti,ab,kw (Word variations have been searched)
#20 (((medication* or medicine* or drug* or prescribing or prescription*) NEAR/3 intervention*)):ti,ab,kw (Word variations have been searched)
#21 ((communication NEAR/5 (tool* or intervention* or system*)):ti,ab,kw (Word variations have been searched)
#22 {OR #6-#12, #17, #18-#21}
#23 #5 and #22
Supplemental material

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#24  MeSH descriptor: [Critical Care] explode all trees
#25  MeSH descriptor: [Intensive Care Units] explode all trees
#26  MeSH descriptor: [Critical Illness] explode all trees
#27  ((ITU or ICU or ICUs or intensive care or critical care)):ti,ab,kw (Word variations have been searched)
#28  #24 or #25 or #26 or #27
#29  #23 and #28

Science Citation Index

#1 TOPIC: ((discharg* or transition* or transfer*))
#2 TOPIC: (((medication* or medicine* or drug* or prescribing or prescription*) NEAR/1 (review* or reconciliation or optimi?ation or system* or error* or discrepance or safety )))
#3 TOPIC: (((medication* or medicine* or drug* prescribing or prescription*) and (adverse NEAR/1 event*))
#4 TOPIC: (((medication* or medicine* or drug* or prescribing or prescription*) NEAR/3 intervention*))
#5 TOPIC: ((communication NEAR/5 (tool* or intervention* or system*))
#6 #5 OR #4 OR #3 OR #2
#7 TOPIC: ((ITU or ICU or ICUs or intensive care or critical care)
#8 #7 AND #6 AND #1

Grey Literature Search

A search of the trial registries International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov was conducted on 4th-5th August 2021. A series of targeted searches for intervention terms such as "medication review" "reconciliation" or "optimization" and setting terms such as "intensive care" or "critical care" were conducted and results retrieved were screened for relevance by the Information Specialist (EEE). 95 trials were found for inclusion consideration.

### Additional File 2: Intervention Study Template for Intervention Description and Replication (TIDieR) Summary

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<tr>
<th>Author/Year</th>
<th>Brief Name</th>
<th>Why</th>
<th>What</th>
<th>Who Provided</th>
<th>How</th>
<th>Where</th>
<th>When and How much</th>
<th>Tailoring</th>
<th>Modificatio ns</th>
<th>How well</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anstey 2019 [54]</td>
<td>Stress Ulceration Prophylaxis (SUP) de-escalation bundle</td>
<td>To improve SUP prescription compliance (including de-prescribing). To reduce medication costs in patients admitted to the intensive care units (ICU)</td>
<td>1. Site-based dissemination and education of locally produced SUP prescribing guidelines for medical staff (including documentation of indication and duration of therapy). 2. ICU pharmacist-led discontinuation of SUP prior to ICU discharge if no clear ongoing indication</td>
<td>ICU pharmacists</td>
<td>All sites had pharmacists present in the ICU in both study periods and used paper-based records throughout for SUP prescription review</td>
<td>ICUs (multicentre)</td>
<td>No information</td>
<td>No information</td>
<td>No information</td>
<td></td>
</tr>
<tr>
<td>Bosma 2018 [13]</td>
<td>Medicines reconciliation on ICU admission and discharge</td>
<td>Many changes are made to a patient’s medication whilst in ICU. When an ICU patient is ready for ward</td>
<td>1. Creation of an accurate medication history list on ICU admission. 2. Creation of an ICU medication list.</td>
<td>ICU pharmacist</td>
<td>Medicines reconciliation on admission included contact with community pharmacy</td>
<td>ICUs (two centres). ICU pharmacists required for admissions, ward rounds and</td>
<td>No information</td>
<td>No information</td>
<td>No information</td>
<td>On how many patients were excluded (e.g., )</td>
</tr>
<tr>
<td>Transfer, there is an increased risk of medication errors as a result of failure to restart important chronic medication and/or potentially inappropriate medication is continued. Medicines reconciliation on ICU admission and discharge can help identify medication changes, medication transfer errors and reduce potential adverse drug events.</td>
<td>Discharge list sent as a section of the ICU discharge letter to the ward physician. 3. ICU pharmacist used medication history to inform advice during ICU ward rounds. 4. ICU medication review, advice and discussion with ICU physician regarding ward medication continuity plan. 5. Ward medication was pre-populated by the ICU pharmacist on the ward e-prescribing system.</td>
<td>Reconciliation done in conjunction with ICU and then ward medical staff and hospital databases information (not stipulated if electronic or telephone) and face to face discussion with patient/relative. Medicines reconciliation then followed up with face-to-face discussion of ICU pharmacist recommendations with ICU medical staff. On ICU discharge the ICU pharmacist and ICU physician discussed the list and pharmacist recommendations.</td>
<td>Planning on ICU to ward electronic prescription discharge. Admission medicines reconciliation 87.3% (185) patients on admission and 68.9% (122) of patients on ICU discharge. Medicines reconciliation on ICU admission took a mean 24.0 (34.3) minutes; on ICU discharge it took a mean 29.4 (42.0) minutes.</td>
<td>Transfer to another hospital, both admission and discharge within the same weekend period and patient’s inability to be counselled in Dutch or English). Quality of medicines reconciliation on ICU admission: Optimal 129 (60.8%); no (proper) conversation 79 (37.3%); poor 4 (1.9%). Quality of ICU discharge medicines reconciliation: Optimal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Methodology</td>
<td>Findings</td>
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<tr>
<td>Buckley</td>
<td>2015</td>
<td>Clinical pharmacist-led intervention can optimise use of SUP and help prevent inappropriate prescribing of SUP</td>
<td>Pharmacists with prescriptive authority for SUP medication with a defined institutional protocol using e-prescribing system with medical staff review and authorisation.</td>
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<tr>
<td>Coon</td>
<td>2015</td>
<td>ICU transfer checklist</td>
<td>Incorporating a standardised checklist into existing transfer documentation would decrease the rate of inaccurate medicines reconciliation by transferring physicians and would reduce unnecessary urinary catheter use.</td>
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| | | | | | | | | | | | 119 (67.2%); no (proper) conversation 4 (2.3%); poor quality 1 (0.6%) |
The standardised documentation would be valued by both transferring and accepting physicians.

**D’Angelo 2019 [57]**

| Antipsychotic discontinuation bundle | An antipsychotic discontinuation algorithm (guideline), supported by a bespoke education programme would provide: (1) audit and feedback data for staff to improve their knowledge of actual versus perceived practice with ICU antipsychotics for delirium, (2) identify potential/

| 1. Education of staff (physicians, nurse practitioner and nurses) on delirium management 2. Antipsychotic discontinuation algorithm. 3. Education for staff (physicians, nurse practitioners, nurses, and clinical pharmacists) Implementation of nonpharmacol | Research team provided education (Pharmacist and medical staff) | Multiprofessional education: Electronic module (bimonthly) & lectures on induction & twice weekly ICU teaching sessions Education. (Nurses): in-services to reach all shifts. At induction for new staff. | ICU | No information | No information | Patients with an evaluable CAM-ICU score in the Before and After groups (35/140) and (24/141), respectively). Before: 65.7% of patients continued on antipsychotics despite a negative CAM-ICU for a minimum of 24 hours.

Before and After groups (35/140) and (24/141), respectively). Before: 65.7% of patients continued on antipsychotics despite a negative CAM-ICU for a minimum of 24 hours.
<p>| Hammon d 2017 [58] | Education on SUP guideline | Education of staff would improve awareness and knowledge of SUP guidelines and implementation thereof, would reduce actual barriers to implementation, and (3) identify changes required to ensure implementation success. Implementation of the bundle would improve patient safety by increasing delirium screening, non-pharmacological management of delirium and reduce inappropriate antipsychotic therapy at transfer from ICU to hospital ward or home. | 1. SUP guideline pocket card on SUP initiation and choice of agent. 2. Education on the SUP materials | Clinical pharmacist | Face to face 5-minute education session, One-off 5-minute education session in Jan 2015. Education | ICU | No information | No information | Due to scheduling constraints, some medical staff that worked night shifts during their first week in prior to ICU transfer, compared with 50% of patients in the After group. |</p>
<table>
<thead>
<tr>
<th>Hatch 2010 [59] (After)</th>
<th>Education on SUP guideline</th>
<th>Staff education, supported by audit and feedback on appropriate SUP use, would reduce inappropriate continuation of SUP at hospital discharge</th>
<th>Hospital SUP guidelines, supported by dissemination of previous audit and feedback results. Pocket guide. Memorandum on SUP distributed to ICU, medicine and surgery medical staff. Education of medical and pharmacy staff on the SUP guidance</th>
<th>Senior physicians to incorporate into training meetings for new medical residents. Pharmacist provided education to pharmacists</th>
<th>Memorandum on SUP communicated via email. Senior physician training via induction meetings for new medical staff. Pharmacist face to face meeting once (October 2006) with education and audit and feedback of previous results</th>
<th>Critical care, medicine, and surgical services medical and pharmacy staff educated</th>
<th>Email of SUP memo. Medical staff education meetings. Pharmacist education session (one)</th>
<th>No information</th>
<th>No information</th>
<th>No information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heselma</td>
<td>Medication</td>
<td>Pharmacists</td>
<td>Hospital</td>
<td>Pharmacist</td>
<td>Medical,</td>
<td>Once on</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Intervention</td>
</tr>
<tr>
<td>ns 2015 [14]</td>
<td>n review of patients transferred from ICU to wards</td>
<td>undertook medication review on the ward within 48 hours of ICU patient transfer. They made recommendations to medical staff when DRPs were identified</td>
<td>pharmacist. There is no formal curriculum for clinical pharmacists in Belgium. The pharmacists in the study had all completed a 6-year course in hospital pharmacy</td>
<td>informed by an e-mail sent automatically to undertake a medication review of the patient upon ward transfer (within 48hrs). Patient cases were discussed in pharmacists’ group meetings at regular intervals. Pharmacists’ recommendations for drug therapy changes were communicated (i) in person to the ward physicians in the intervention group; (ii) if necessary, via a formal e-mail to the newly admitted wards</td>
<td>surgical or geriatric wards of 3 centres.</td>
<td>admission to the ward from ICU (within 48 hours)</td>
<td>information</td>
<td>information</td>
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<tr>
<td>298</td>
<td>received intervention (3 did not as were discharged)</td>
<td>Control: 289 received control (10 did not on ethical grounds)</td>
<td>BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s) BMJ Qual Saf</td>
<td>doi: 10.1136/bmjqs-2021-013760–14.</td>
<td>2022;BMJ Qual Saf, et al. Bourne RS</td>
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<tr>
<td>Kram 2019 [60]</td>
<td>Electronic handover tool</td>
<td>A handover tool would enhance clinical pharmacist communication, review and transition continuity of antipsychotics therapy for ICU patients (for non-mental health indications), thereby potentially reducing inappropriate antipsychotic therapy in</td>
<td>Electronic handover tool developed and integrated into the e-prescribing system. Formalised education about ICU delirium, consensus guideline on pharmacologic management of delirium. Education underpinned with pre-intervention</td>
<td>ICU pharmacists provided specialised pharmacy services, participated in daily ward rounds, and were responsible for clinical verification for their respective ICUs</td>
<td>Education was provided face to face. Electronic handover to pharmacists both within ICU care and on ICU to ward transfers via the e-prescribing system. The status of the handoff remained open until the AAP was</td>
<td>Handover commenced on ICU and continued onto the ward if the handover episode remained open</td>
<td>All clinical pharmacists reviewed electronic handoffs daily (0700-2330h) for their designated patients as part of their normal clinical activities</td>
<td>No information</td>
<td>No information</td>
<td>Electronic handovers were generated 66.7% (150) patients in the post-intervention group. The majority of patients (55.3%) with a discharge prescription in the postintervention group were not followed by a service-</td>
</tr>
<tr>
<td><strong>Medlock 2011</strong>  [61]</td>
<td><strong>Electronic discharge letter for ICU patients</strong></td>
<td>The discharge letter is the primary means of communication at patient discharge. Improving timely completion of discharge letters would improve discharge communication and reduce risks to patient safety.</td>
<td>ICU discharge e-letter (to ward &amp; GP). Policy change by ICU management team so all ICU patients to have e-letters that go with patient to the ward. Responsibility for completion of the letter automatically assigned and visible. Letter template to aid completion</td>
<td>ICU medical staff are responsible for finalising the letters</td>
<td>E-letter with electronic allocation and email reminders</td>
<td>ICU with electronic clinical information system</td>
<td>Uncompleted letters on ICU patient discharge prompts weekly email reminder for designated medical staff member assigned responsibility</td>
<td>No information</td>
<td>Improvememt directive by management team in February of 2006. ICU team agreed to plan and designed the software and letter templates. The e-letter was tested in October - December 2006 with roll out on 1 January 2007</td>
<td>Percentage of ICU patients with a completed letter on discharge increased from 2.5% (before phase) to 80% in the 34 months after phase. By month 3, 89.9% of patients had a discharge letter completed on time</td>
</tr>
<tr>
<td><strong>Meena 2015</strong>  [47]</td>
<td><strong>Education of medical staff on SUP</strong></td>
<td>Improving medical staff knowledge of SUP in ICU patients would improve the use of SUP and reduce</td>
<td>Pre-rotation questionnaire followed by didactic education session on SUP for ICU medical staff (House)</td>
<td>Didactic education sessions were conducted monthly by the critical care</td>
<td>Didactic education session provided for medical staff</td>
<td>No information</td>
<td>Single education session provided on monthly basis</td>
<td>No information</td>
<td>No information</td>
<td>No information</td>
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</table>
inappropriate continuation, including at patient transition from ICU

<table>
<thead>
<tr>
<th>Authors</th>
<th>Institution</th>
<th>Description</th>
<th>Methodology</th>
<th>Findings</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parsons Leigh 2020 [48]</td>
<td>ICU e-transfer tool</td>
<td>Employment of an evidence-informed ICU-specific e-transfer tool would improve completion and communication of care for ICU patients on ward transition</td>
<td>The final e-transfer tool had 8 sections: Visit Data, Goals of Care, Allergy and Intolerances, Diagnoses and Visit Issues, Course in ICU, Investigations, Medications, and Discharge to Home/Community. Used a combination of automated fields and free text fields</td>
<td>ICU medical staff (residents) used the e-transfer tool. Supported by 15-minute education session pre-use. Multiprofessional implementation team developed the e-transfer tool. Included medical staff (ICU and ward), outreach nurse, the CIS physician lead, clinical operations</td>
<td>On ICU pre-transfer</td>
</tr>
<tr>
<td>Pavlov 2014 [49]</td>
<td>Medicines reconciliation on hospital admission and ICU discharge</td>
<td>Medicines reconciliation provides a more accurate pre-admission medication list reducing medication errors. Undertaking medicines reconciliation on patient admission and discharge, would reduce inappropriate continuation of SUP and bronchodilators</td>
<td>Medicines reconciliation including the patients/representative with a review of previous discharge notes and local out-patient pharmacy records via a database. Pre-admission medicines entered on the e-medical record for review and approval within 48 hours. Medical staff undertook</td>
<td>Pharmacy technician compiled meds re-entered on electronic medical record-reviewed and modified/approved by the admitting medical staff within 48 hours. Medical staff reviewed Emergency room and ward</td>
<td>Interviewed subjects, or representatives when required, and reviewed previous discharge notes and local out-patient pharmacy records available through a local database. Medical staff review</td>
</tr>
<tr>
<td><strong>Pronovost 2003</strong> [50]</td>
<td><strong>Medicines reconciliation on ICU discharge</strong></td>
<td><strong>Medicines reconciliation in ICU discharge reduces medication errors</strong></td>
<td><strong>Standardised paper medicines reconciliation forms. All ICU nurses were educated on use of the discharge survey which was available on the front of every admissions chart. Instructions on completions were also included in the research.</strong></td>
<td><strong>ICU nurses completed the medicines reconciliation forms made available by ICU ward clerks.</strong></td>
<td><strong>Completion of a discharge survey that identified specific types of possible medication errors that prompted discussion with an ICU physician to resolve if needed.</strong></td>
</tr>
<tr>
<td><strong>Stuart 2020</strong> [53]</td>
<td>Antipsychotic de-escalation protocol</td>
<td>Pharmacist-led protocol would increase the effectiveness of discontinuation of antipsychotics for ICU delirium and reduce the inappropriate continuation at Antipsychotic de-escalation guideline for resolved ICU delirium support by education for ICU and ward-based pharmacists. A collaborative Pharmacists (ICU and hospital ward (internal medicine)) Pharmacists were trained on the use of the discontinuation protocol in in-service training sessions. Pharmacists ICUs (ICU patients directly discharged from hospital) and internal medicine hospital wards ICU pharmacists attend daily multiprofessional ward rounds (Monday-Friday)</td>
<td>No information</td>
<td>No information</td>
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</tr>
<tr>
<td>Tasaka 2014 [51]</td>
<td>Interprofessional bundle to reduce the overutilisation of SUP</td>
<td>Guideline and education would inform SUP practice, reducing inappropriate continuation. Pharmacist-led intervention would improve the quality of SUP review and utilisation</td>
<td>The SUP guideline was promoted by publication in hospital newsletters, emails to medical staff, development of facilitator guides to use during teaching rounds and presentation to various clinician groups. Education targeted at surgery, medicine and anaesthesia</td>
<td>Multi-professional team (pharmacists, physicians, nurses, and dieticians) planned and developed a bundled approach to reduce the overutilisation of SUP in adult ICU patients. ICU pharmacists undertook SUP medication reviews as Pharmacists-led SUP intervention on the ICU with recommendations for medical staff on SUP therapy</td>
<td>ICU pharmacist SUP recommendations made in person during their patient rounds to the ICU medical staff, or made via text page or phone call</td>
</tr>
<tr>
<td>Zeigler 2008 [52]</td>
<td>Medicines reconciliation on admission and at patient transition interfaces, would decrease the incidence of medication errors</td>
<td>Medicines reconciliation consisted of a medication history entered into the e-health record, reviewed by the admitting physician. Upon level of care transfers (eg, ICU to non-ICU unit) medication profiles are</td>
<td>Pharmacists and nurses undertook the medicines reconciliation with medical staff review at each transfer point</td>
<td>Medicines reconciliation on individual patient basis. Upon level of care transfer (eg., ICU to non-ICU unit) or hospital discharge, medication profiles are printed and</td>
<td>On admission and upon level of care transfer (e.g., ICU to non-ICU unit) or hospital discharge</td>
</tr>
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printed and reviewed by the primary physician. Prior to implementation of medicines reconciliation, education of clinical staff (medical, nursing, pharmacy) on process and roles was completed. Education was done by classes, a Web-based training module, presentations at hospital committee meetings, and one-to-one communication.

reviewed by the lead physician, and existing agents are ordered to be either discontinued or resumed.

<table>
<thead>
<tr>
<th>Table S1: Summary of intervention details using TIDieR template [41]</th>
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<tbody>
<tr>
<td>DRPs: Drug-related problems; ICU: Intensive care unit; SUP: Stress ulceration prophylaxis</td>
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Additional File 3: Economic outcomes and Summary of findings

Economic Evaluations

Four studies included an economic evaluation (Table S4) (13,54,55,59). However, only three of the studies included details for ICU patients on the interface of ward transfer (13,54,59). Two studies focused on the cost avoidance of reducing inappropriate continuation of SUP (54,59). Bosma et al (13), calculated the cost-benefit of the pharmacist-led medicines reconciliation programme in their two-centre Dutch study. They reported a positive cost–benefit ratio of 2.48, indicating a potential net cost–benefit of 2018 €103 per patient based on intervention costs and pADEs prevented.
<table>
<thead>
<tr>
<th>Author/ Year/ Country</th>
<th>Medication Outcome(s)</th>
<th>Methods used to identify medication outcome(s)</th>
<th>Patient Outcomes</th>
<th>Economic Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anstey 2019 [54] Australia</td>
<td>Inappropriate stress ulcer prophylaxis (SUP) continuation (Hospital discharge). Before: 78/184 (42.4%) versus Vs. After: 11/143 (7.7%) p&lt;0.001</td>
<td>Standardised data extraction form of patients on SUP without an indication (from evidence-based SUP indication list) [prospective chart review completed by medical staff not involved in prescribing of SUP]</td>
<td>No between group comparison of gastro-intestinal (GI) bleed, pneumonia or Clostridium difficile rates</td>
<td>SUP deprescribing data extrapolated to pan-Australia. Based on 2016 data, the additional lifetime cost (assuming 10-year endurance) of inappropriate SUP continuation post-ICU in a year is AUD $20.82 million. Under the shorter scenarios of two- or five-year continuation, this figure reduces proportionally to AUD $4.16 million and AUD $10.41 million, respectively</td>
</tr>
<tr>
<td>Bosma 2018 [13] Netherlands</td>
<td>Medication Errors (MEs) on transfer (ICU discharge). Before: 73.9% of 203 patients had ≥1 MEs Vs. After: 41.2% of 177 patients. A reduction of 44.2%. Odds Ratio adjusted (OR adj) 0.24 [95% CI 0.15–0.37], adjusted for severity of illness</td>
<td>ME at discharge was an unintentional discrepancy between the actual patient medication chart compared to the best possible general ward medication list (24 hours after the ICU discharge). When possible, this included a ward physician discussion [completed by two ICU pharmacists with crosschecking of data]. All MEs were validated as part of the potential adverse drug events (pADE) assessment. All MEs were randomly assigned and assessed by two ICU healthcare professionals independently, reaching consensus when required</td>
<td>pADE on transfer. Before: Proportion of patients with a pADE ≥ 0.01 was 69.5% of 203 patients Vs. 36.2% of 177 patients, a reduction of 47.9%. OR adj 0.26 [95% CI 0.17–0.40] adjusted for severity of illness</td>
<td>Positive cost–benefit ratio = 2.48, indicating a potential net cost–benefit of €103 per patient. Costs of the intervention were €7476 at admission and €7256 at discharge. At admission 7.33 pADEs were prevented, leading to a cost avoidance of €7911 at admission. At discharge 26.59 pADEs were prevented, leading to a cost avoidance of €28,687. The cost–benefit remained positive in the sensitivity analysis</td>
</tr>
<tr>
<td>Buckley 2015 [55] USA</td>
<td>Inappropriate SUP continuation (ICU discharge). Before: 67.8% (118/174) patients Vs. After: 38.9% (65/167) patients, p&lt;0.001</td>
<td>SUP was considered inappropriate in ICU patients without any major risk factors from a standardised list or pre-admission therapy. SUP appropriateness assessed retrospectively by research team chart review</td>
<td>No between group comparison of upper GI bleed, pneumonia or Clostridium difficile rates</td>
<td>ICU and ward SUP costs were compared in Before and After periods, but these did not specifically relate to ICU patient hospital discharge data</td>
</tr>
<tr>
<td>Coon 2015 [56]</td>
<td>Patient transfers with active IV antihypertensives or</td>
<td>Medication reconciliation (med rec) of intravenous (IV) antihypertensives and</td>
<td>No difference in mean length of stay (LOS) on hospital ward after</td>
<td>None</td>
</tr>
<tr>
<td>Country</td>
<td>Description</td>
<td>Methodology</td>
<td>Findings</td>
<td>Notes</td>
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<tr>
<td>USA</td>
<td>Vasopressors (surrogate marker of medicines reconciliation) [ICU discharge]. Before: 36.2% (47/130) of patients Vs. After: 9.9% (13/131), p=0.001</td>
<td>Vasopressors was prospectively assessed. Medications reconciliation was deemed not undertaken if the e-prescribing system had an active prescription for either IV therapy groups on ICU discharge</td>
<td>ICU transfer (5 days in both groups, p=0.31). No between group difference (Before Vs. After) in adverse events (as measured by ICU readmissions (4(3) Vs. 5(4); p=0.74) or rapid response team calls (2(2) Vs. 4(3); p=0.69))</td>
<td>None</td>
</tr>
<tr>
<td>D'Angelo 2019 [57] USA</td>
<td>Inappropriate antipsychotic continuation [ICU discharge]. After: OR 0.47 [95%CI 0.26-0.86]</td>
<td>Retrospective data collection from the patient medical chart review including delirium status at set time periods. Antipsychotic medication exposure was collected for each patient. Antipsychotics were recommended to be stopped once the patient was delirium-free for 48 hours</td>
<td>No between group comparison of hospital LOS of ICU transfer patients</td>
<td>None</td>
</tr>
<tr>
<td>Hammon d 2017 [58] USA</td>
<td>Inappropriate SUP continuation [ICU discharge]. Before: 60% (61/101) patients Vs. After: 53.4% (63/118) patients, p=0.297</td>
<td>Appropriateness of SUP was assessed by chart review at the time of transfer from the ICU. Assessment was against set guideline criteria for SUP clinical appropriateness.</td>
<td>No difference in adverse events related to SUP between the intervention periods. E.g., pneumonia, 5(5%) before vs. 6(5%) after; p&gt;0.99</td>
<td>None</td>
</tr>
<tr>
<td>Wohlt 2007 [62] (Before) Hatch</td>
<td>Inappropriate SUP continuation [ICU discharge]. Before: 48% (189/394) patients Vs. After: 23.6% (84/356)</td>
<td>Retrospective review of patient electronic medical records, pharmacy systems and discharge records. Assessment of SUP appropriateness against approved local guidelines.</td>
<td>None</td>
<td>Single ICU data indicated the reduction in inappropriate SUP drug use by 64.3% (After), leading to over USD $200,000</td>
</tr>
<tr>
<td>Year</td>
<td>Study</td>
<td>Country</td>
<td>Intervention Details</td>
<td>Control Details</td>
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<tr>
<td>2010</td>
<td>[59]</td>
<td>USA</td>
<td>Inappropriate SUP continuation [Hospital discharge]. Before: 24.4% (96/394) patients Vs. After: 8.7% (31/356) patients</td>
<td>Inappropriate SUP continuation [Hospital discharge]. Before: 24.4% (96/394) patients Vs. After: 8.7% (31/356) patients</td>
</tr>
<tr>
<td>Heselmanns 2015</td>
<td>[14]</td>
<td>Belgium</td>
<td>Incidence of drug-related problems (DRPs). Ward stay within 48hrs of ICU transfer. Intervention: 54.1% (203/375) DRPs were adjusted on time Vs. Control: 12.8% (47/368). ORadj 15.6 [95%CI 9.4–25.9] after adjustment for differences in types of DRPs between the groups. Intervention effect by clinical impact category of DRPs. Major (n=184): 11.3 [95%CI 4.9–25.4]; Moderate (n=97): 19.6 [95%CI 5.9–64.4]; Minor (n=396): 14.1 [95%CI 6.9–28.6]; None (n=66): 0.9 [95%CI 0.2–3.1].</td>
<td>None</td>
</tr>
<tr>
<td>Kram 2019</td>
<td>[60]</td>
<td>USA</td>
<td>Inappropriate antipsychotic continuation [Hospital discharge]. Before: 19.5% (26/133) of patients Vs. After: 11.6% (26/225) of patients</td>
<td>Atypical antipsychotic prescription on discharge was deemed inappropriate (by consensus criteria) if the patient was documented at their baseline mental status in the medical record, or if there was no documented indication for continuation of antipsychotic therapy. Data collected by pharmacists from the electronic prescribing system.</td>
</tr>
<tr>
<td>Medlock 2011</td>
<td>[61]</td>
<td>Netherlands</td>
<td>Completion of ICU discharge letter (including medication information) [ICU discharge]. Before: 2.5% of 1872 patients Vs. After: 80% of 4951 patients.</td>
<td>Data on electronic letter completion were taken from the patient data management system (PDMS). Dictated letters data were collected from matching the patient PDMS and hospital letters databases.</td>
</tr>
<tr>
<td>Study</td>
<td>Setting</td>
<td>Intervention</td>
<td>Outcome Measures</td>
<td>Additional Information</td>
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<td>-------</td>
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<tr>
<td>Meena 2015 [47] USA</td>
<td>Inappropriate SUP continuation [ICU discharge]. Before: 68.7% (68/99) of patients Vs. After: 36.5% (42/115) of patients, p&lt;0.001. Inappropriate SUP continuation [Hospital Discharge]. Before: 23.9% (22/92) patients vs. After: 16.5% (18/109) of patients, p=0.19</td>
<td>Retrospective chart review by research team. Inappropriate SUP defined by not meeting local guidelines requiring at least one major or minor SUP indication.</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Parsons Leigh 2020 [48] Canada</td>
<td>Transfer documentation of active medications [ICU discharge]. Before (dictation): 80% (24/30) Vs. After (electronic e transfer tool): 97% (29/30) patients, p=0.044 Transfer documentation of medicines reconciliation. Before (dictation): 27% (8/30) Vs. After (etransfer tool): 53% (16/30) patients, p=0.035</td>
<td>Standardised data collection form capturing completion rates of 8 essential transfer elements (including active medications and medicines reconciliation). Binary score, either present or absent for dictated and etransfer tools.</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Pavlov 2014 [49] USA</td>
<td>Inappropriate SUP continuation [ICU discharge]. Before Intervention ORadj 2.5 [95%CI 1.4–4.7] Inappropriate bronchodilator</td>
<td>Data extracted from patient medical records. Medication data collated from the dictated admission and discharge notes (Before) or pharmacy technician/ medical staff pre-admission list and discharge list from the nurse</td>
<td>ICU patient mortality rate was lower in the After group compared to Before group 13.2 vs. 20.6%, p=0.006. However, mortality rate not clearly linked to the</td>
<td>None</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Country</td>
<td>Intervention</td>
<td>Before</td>
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</tr>
<tr>
<td>Pronovost 2003</td>
<td>2003</td>
<td>USA</td>
<td>None</td>
<td>Before: 94% (31/33) in 2-week baseline Vs. After: average 5% per week over 22 weeks</td>
</tr>
<tr>
<td>Stuart 2020</td>
<td>2020</td>
<td>USA</td>
<td>None</td>
<td>Before: 35% (21/60) Vs. After: 35.9% (23/64) of patients</td>
</tr>
<tr>
<td>Tasaka 2014</td>
<td>2014</td>
<td>USA</td>
<td>None</td>
<td>Before (Post-CPOE); 8% (6/74) Vs. After: 4% (2/50), p=0.54</td>
</tr>
<tr>
<td>Zeigler 2008</td>
<td>2008</td>
<td>USA</td>
<td>None</td>
<td>Before Intervention ORadj 2.4 [95%CI 0.98–5.9]. Inappropriate continuation of Either (SUP or bronchodilator). Before 46/253 (18.2%); After 24/291 (8.2%), p=0.006</td>
</tr>
</tbody>
</table>
Before: 85% (45/53) of patients
Vs. After: 79% (48/61) of patients, p=0.393.
Inappropriate SUP continuation
[Hospital discharge].
Before: 14% (6/44) of patients
Vs. After: 23% (10/43) of patients, p=0.247

Med rec data available from the electronic medical record. SUP was considered inappropriate if the patients did not have at least 1 major risk factor or 2 minor risk factors from a locally agreed guideline.

Table S2: Summary of study findings and methods used to identify medication outcome(s)

| DRPs: Drug-related problems; ICU: Intensive care unit; eTransfer: Electronic transfer; GI: Gastro-Intestinal; LOS: Length of stay; MEs: medication errors; pADEs: OR_adj: Odds Ratio – adjusted; pADEs: Potential adverse events; SUP: Stress Ulceration prophylaxis; Vs.: Versus. |
### Additional File 4: Risk of Bias and GRADE assessments

**Figure S1. Robvis representation of ROBINS-I risk of bias assessments of non-randomised controlled trial studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6</th>
<th>D7</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anstey 2019 [54]</td>
<td>X</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>Bosma 2018 [13]</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Buckley 2015 [55]</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>Coon 2015 [56]</td>
<td>X</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>D'Angelo 2019 [57]</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Hammond 2017 [58]</td>
<td>X</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>Hatch 2010 [59]</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>Kram 2019 [60]</td>
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<td>+</td>
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<td>-</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>Medlock 2011 [61]</td>
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<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Meena 2015 [47]</td>
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<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>Parsons Leigh 2020 [48]</td>
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<td>-</td>
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<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>Pavlov 2014 [49]</td>
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<td>+</td>
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<td>-</td>
<td>-</td>
<td>X</td>
</tr>
<tr>
<td>Pronovost 2003 [50]</td>
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<td>+</td>
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<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Stuart 2020 [53]</td>
<td>X</td>
<td>+</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>Tasaka 2014 [51]</td>
<td>X</td>
<td>+</td>
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<td>-</td>
<td>-</td>
<td>+</td>
<td>X</td>
</tr>
<tr>
<td>Zeigler 2008 [52]</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>X</td>
</tr>
</tbody>
</table>

**Domains:**
- D1: Bias due to confounding.
- D2: Bias due to selection of participants.
- D3: Bias in classification of interventions.
- D4: Bias due to deviations from intended interventions.
- D5: Bias due to missing data.
- D6: Bias in measurement of outcomes.
- D7: Bias in selection of the reported result.

**Judgement:**
- Critical
- Serious
- Moderate
- Low
Figure S2. Robvis representation of ROB2.0 risk of bias assessments of the randomised controlled trial study
Figure S3. Funnel plot of the treatment effect estimates from individual studies included in the meta-analysis.
<table>
<thead>
<tr>
<th>No of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Odds Ratio (OR) (95% CI)</th>
<th>Certainty</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main meta-analysis. All de-escalation studies - ICU discharge inappropriate medication therapy</strong></td>
<td>9 observational studies</td>
<td>very serious</td>
<td>not serious</td>
<td>serious</td>
<td>not serious</td>
<td>strong association</td>
<td>OR 0.45 (0.31 to 0.63)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Main meta-analysis. All de-escalation studies - Hospital discharge inappropriate medication therapy</strong></td>
<td>9 observational studies</td>
<td>very serious</td>
<td>serious</td>
<td>serious</td>
<td>not serious</td>
<td>strong association</td>
<td>OR 0.39 (0.2 to 0.76)</td>
<td>VERY LOW</td>
</tr>
<tr>
<td><strong>Sub-group meta-analysis. Multicomponent de-escalation studies - ICU discharge inappropriate medication therapy</strong></td>
<td>3 observational studies</td>
<td>very serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>strong association</td>
<td>OR 0.37 (0.23 to 0.59)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Subgroup meta-analysis. Multicomponent de-escalation studies - Hospital discharge inappropriate medication therapy</strong></td>
<td>6 observational studies</td>
<td>very serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>strong association</td>
<td>OR 0.26 (0.13 to 0.55)</td>
<td>MODERATE</td>
</tr>
<tr>
<td><strong>Subgroup meta-analysis. Single component de-escalation studies - ICU discharge inappropriate medication therapy</strong></td>
<td>5 observational studies</td>
<td>very serious</td>
<td>serious</td>
<td>not serious</td>
<td>not serious</td>
<td>strong association</td>
<td>OR 0.42 (0.24 to 0.74)</td>
<td>LOW</td>
</tr>
<tr>
<td><strong>Subgroup meta-analysis. Single component de-escalation studies - Hospital discharge inappropriate medication therapy</strong></td>
<td>3 observational studies</td>
<td>very serious</td>
<td>serious</td>
<td>not serious</td>
<td>None</td>
<td></td>
<td>OR 0.77 (0.16 to 3.74)</td>
<td>VERY LOW</td>
</tr>
</tbody>
</table>

**Table S3: Meta-analysis GRADE assessments**

**Explanations**

1. High-risk of bias on ROBINS-I (downgraded 2 levels)
2. Significant variability in intervention components and timing of delivery (downgraded 1 level)
3. Large effect – OR <0.5 (upgraded 1 level)
4. Heterogeneity ($I^2 \geq 75\%$) (downgraded 1 level)