E.1 Regular ward-based pharmacist support

Study	Claus 2014[13]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcomes: in-hospital mortality, adverse drug events) **Study design:** Randomised controlled trial (RCT) with propensity score matched before-and-after cohort. **Approach to analysis:** comparative cost analysis was undertaken to calculate the difference between pharmaceutical investment (intervention cost) and mean daily ICU drug cost and the cost: benefit ratio of the intervention. Propensity score matched before and after cohort were also used (matching variables including age, main diagnostic category, ICU length of stay, in-hospital mortality and severity index). The results reported here are for the	**Population:** Critically ill patients (>16 years of age and with minimum length of ICU stay of 2 days) in a 22-bed, surgical ICU at Ghent University Hospital, Belgium. **Cohort settings: (n=135[randomised], 109[matched, before-group] and 111[matched after-group])** Mean age: Intervention 1= 58 years Intervention 2= 61.1 years Male: Intervention 1= 58.3% Intervention 2= 74.4% **Intervention 1: (n=60)** No clinical pharmacist direct involvement in patient care. Pharmacist drug recommendations were	**Total costs (mean per patient)[(a)]:** Intervention 1: £354 Intervention 2: £195 Incremental (2−1): -£159 (95% CI: NR; p=NR) **Pharmacist time costs (mean per patient):** Incremental (2−1): £13 (95% CI: NR; p=NR) **Total drug costs (mean per patient):** Intervention 1: £354 Intervention 2: £182 Incremental (2−1): -£172 (95% CI: NR; p=0.87) **Currency & cost year:** 2013 euros (presented here as 2013 UK pounds[(b)]) **Cost components incorporated:**	**In-hospital mortality:** Intervention 1: 18.3% Intervention 2: 24% Incremental (2−1): 5.7% (95% CI: NR; p=0.53) **Adverse events rate (mean per patient):** Intervention 1: 0.12 Intervention 2: 0.19 Incremental (2−1): 0.07 (95% CI: NR; p=0.34)	**ICER (Intervention 2 versus Intervention 1):** The paper reports unadjusted mean benefit: cost ratio: 25:1 (95% CI: -5:1 to 94:1) Taking outcomes into account: Clinical pharmacist intervention less costly and less effective **Analysis of uncertainty:** - RCT analysis: bootstrapping was used to generate replications of the cost differences. Mean cost-benefit ratio was calculated from these replications. The percentage of replications that showed benefit :cost ratio ≥1 was calculated. In the base case analysis, the intervention was found to be cost-beneficial in 53.8% of the replications. - Matched analysis: No significant difference in drug costs was found when comparing the before-group or the after-group with intervention 2 group (p=0.94 and p=0.65, respectively) or intervention 1 group (p=0.37 and 0.12, respectively). **-Adjustment for patient characteristics**: Analysis was repeated excluding liver transplantation and tracheostomy. In both cases, the difference in drug costs remained

randomised part of the study. **Perspective:** Belgian healthcare payer **Follow-up:** ICU stay **Treatment effect duration:** same as follow-up **Discounting:** Costs: n/a; Outcomes: n/a	documented by the pharmacist but not communicated to the ICU caregiver. **Intervention 2: (n=75)** A clinical pharmacist is directly involved in patient care, providing active recommendations regarding drug therapy and follow-up. The current pharmacy staff carried out the recommendation (1 junior pharmacist with basic level clinical pharmacy and 1 senior pharmacist with advanced training in clinical pharmacy). Pharmacist recommendations focused on antimicrobial therapy, total parenteral nutrition, drugs with potential for significant interactions, drugs with equal intravenous and oral bioavailability, drugs requiring dose adaptations or follow-up.	Pharmacist time (chart analysis, consultation, researching and follow-up) Drug costs		non-significant (p=0.78 and 0.88 respectively) and the intervention was cost beneficial in 62% and 74.1% of the replications, respectively. **-Excluding outlier ICU drug costs (> 2SD [standard deviation]):** Difference in drug costs was significant after excluding patients with outlier drug costs (p<0.001) in the randomised analysis. The intervention was cost beneficial in 95.2% of the replications. In the matched analysis (comparing the matched before- and after-groups with the intervention 1), the difference in drug costs was significant (p<0.001 for both groups). This showed high baseline expenses which may have reduced the influence of the clinical pharmacy service.
Data sources				
Health outcomes: data collected during the before and after periods on adverse drug events and in-hospital mortality during the ICU stay. **Quality-of-life weights:** n/a. **Cost sources:** Local sources were used of pharmacist time (gross salary of Ghent University Hospital pharmacist with 5 years' experience). ICU drug costs were based on national tariff prices (RIZIV-INAMI).				
Comments				

Source of funding: NR **Applicability and limitations:** QALYs were not used as an outcome measure and only costs and cost savings were included as outcomes. Some uncertainty regarding the applicability of resource use and costs from Belgium (2013) to current NHS context. The intervention is delivered by a junior and a senior clinical pharmacist; which may not be the same as in NHS hospitals. The study is a comparative cost analysis with no health outcomes. The costs included were only pharmacist time and ICU drug costs while the cost of hospital stay and other staff time were not included. The study follow-up is short (ICU stay) and may not capture the difference in all relevant costs. Limited sensitivity analysis is reported.

Overall applicability(c): partially applicable **Overall quality[(d)]:** potentially serious limitations

Abbreviations: CCA: cost-consequences analysis; 95% confidence interval; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; n/a: not applicable; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years.

(a) Calculated by NGC.

(b) Converted using 2013 purchasing power parities.[50].

(c) Directly applicable/Partially applicable/Not applicable.

(d) Minor limitations/Potentially serious limitations/Very serious limitations.

Study	**Ghatnekar 2013[20]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Decision tree model **Approach to analysis:** Probabilistic decision tree model to assess the cost utility of the study intervention. The model focused on prevention of medication error as an outcome. The occurrence of medication errors was linked to increased resource use in order to model the downstream cost implications of treatments.	**Population:** Elderly inpatients **Cohort settings:** Mean age: NR Male: NR **Intervention 1:** Standard care (not defined). **Intervention 2:** Multidisciplinary team including clinical pharmacist undertakes systematic medication review and reconciliation from admission to discharge (the Lund Integrated Medicines	**Total costs (mean per patient)** Intervention 1: £520 Intervention 2: £239 Incremental (2−1): -£280 (95% CI: NR; p=NR) **Currency & cost year:** 2009 euros (presented here as 2009 UK pounds[(b)]) **Cost components incorporated:** Pharmacist time Physician time Nurse time Hospital readmissions	**QALYs (mean per patient):** Intervention 1: -0.009 Intervention 2: -0.004 Incremental (2−1): 0.005 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Clinical pharmacist intervention dominant **Analysis of uncertainty:** Results were presented separately for the admission and discharge parts of the model. For the admission part, the LIMM intervention was dominant with lower cost (incremental cost: -£225) and QALY gain (0.004) For the discharge part, the LIMM intervention was also dominant with lower cost (incremental cost: -£54) and QALY gain (0.001) A number of probabilistic sensitivity analyses were reported: -assuming no quality control of the discharge

Perspective: Swedish healthcare **Follow-up**: 3 months **Treatment effect duration[(a)]:** 3 months **Discounting:** Costs: n/a ; Outcomes: n/a	Management [LIMM])	Outpatient visits		medication report - reduction in hospitalisation cost by 50% -hospitalisation cost 38% higher in intervention arm -admission part probability for hospitalisation in intervention arm increased to 100% -intervention cost (time) 50% higher -cost (time) for physicians and nurses administration reduced by 50% All SAs found the LIMM model to be dominant.
Data sources				
Health outcomes: Relative effectiveness estimates were based on linked clinical studies that were conducted to evaluate the intervention. **Quality-of-life weights:** EQ-5D UK tariff utility data were taken from the literature and supplemented by assumptions regarding QALY loss due to hospitalisation and outpatient visits. **Cost sources:** Costs were based on actual resource use reported in patient charts at Skane University Hospital in Lund, Sweden, in addition to data collected in a series of studies conducted at Swedish hospitals. Costs of hospital readmissions were based on hospital accounting data as well as the nurse, pharmacist and physician time unit cost.				
Comments				
Source of funding: Apoteket Farmaci AB (state owned pharmacy company with commercial interest in disseminating the LIMM model) **Applicability and limitations:** The standard care arm in the study is not clearly described. Some uncertainty regarding the applicability of resource use and costs from Sweden (2009) to current NHS context. Changes in quality of life are based on the literature and assumptions and not reported directly from patients. The model has a short time horizon and does not capture differences in downstream costs and outcomes between the comparators. The baseline and relative treatment effectiveness estimates are based on a series of non-randomised studies conducted to evaluate the LIMM model and source the input parameters for the model, hence by definition, does not reflect all evidence in the area. Local costs appear to have been used and it is not clear whether these costs reflect national costs. A potential conflict of interest might exist given that the study is funded by a pharmacy company with commercial interest in disseminating the LIMM model.				
Overall applicability[(c)]: partially applicable **Overall quality[(d)]:** potentially serious limitations				

Abbreviations: CUA: cost–utility analysis; 95% CI: 95% confidence interval; ED: emergency department; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years; SA: sensitivity analysis.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long?

(b) Converted using 2009purchasing power parities.[50]

(c) Directly applicable/Partially applicable/Not applicable.

(d) Minor limitations/Potentially serious limitations/Very serious limitations.

Study	Gillespie 2009[21]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: survival) **Study design:** Randomised controlled trial (RCT) **Approach to analysis:** Within-trial analysis of resource use and cost data. Logistic regression analysis of binary outcomes using odds ratios, COX proportional hazards model for survival analysis using relative risks, linear regression analysis for continuous outcomes and Poisson regression analysis for incidence. The cost of the intervention was calculated based on pharmacist time and its unit cost. Incremental cost was calculated as the difference between the cost of hospital and ED visits and the intervention cost. **Perspective:** Swedish healthcare **Follow-up**: 12 months **Treatment effect duration[(a)]:** 9 months **Discounting:** Costs: n/a ; Outcomes: n/a	**Population:** Elderly inpatients (80 years or older) admitted to 2 acute internal medicine wards at a University Hospital of Uppsala, Sweden. **Cohort settings: (n=368)** Mean age: Intervention 1: 87.1 years Intervention 2: 86.4 years Male: Intervention 1: 40.3% Intervention 2: 42.3% **Intervention 1: (n=186)** No pharmacist involvement in the healthcare team at the ward level. **Intervention 2: (n=199)** Pharmacist present on the ward. Duties included taking part in the ward rounds, documenting medication history, and discharge counselling and contacted patients 2 months after discharge for a follow-up. The intervention was delivered on **weekdays between 8 am and 4 pm**. Pharmacists had taken postgraduate courses in clinical pharmacy.	**Total costs (mean per patient) including intervention cost** Intervention 1: £6,630 Intervention 2: £6,508 Incremental (2−1): -£122 (95% CI: NR; p=NR) **Currency & cost year:** 2008 Swedish Kroners converted to US dollars (presented here as 2008 UK pounds[(b)]) **Cost components incorporated:** Pharmacist time Hospital readmissions and ED visits	**Mortality:** Intervention 1: 61/186 (32.3%) Intervention 2: 57/182 (31.3%) Incremental (2−1): -1% (95% CI: NR; p=0.82)	**ICER (Intervention 2 versus Intervention 1):** Clinical pharmacist intervention dominant **Analysis of uncertainty:** None reported
Data sources				
Health outcomes: Within-trial analysis of hospital readmissions and ED visits data from the hospital's patient administrative system over a period of 12 months follow-up. **Quality-of-life weights:** n/a. **Cost sources:** The main source of cost data was the hospital's patient administrative system, so likely to be local unit costs. No source is				

given for the unit costs of pharmacist time.
Comments
Source of funding: Institutional and governmental funding. **Applicability and limitations:** QALYs were not used as an outcome measure. Some uncertainty regarding the applicability of resource use and costs from Sweden (2008) to current NHS context. The intervention is delivered by pharmacists with postgraduate training in clinical pharmacy but no specialist status which may not reflect the situation in UK hospitals. Relative effectiveness evidence is based on a single RCT, so by definition does not reflect all evidence in the area. Follow-up for 12 months which may not capture all relevant costs and outcomes. Primary care visits, medication costs and cost of other staff time were not included in the analysis. No sensitivity analysis is reported.
Overall applicability[(c)]: partially applicable **Overall quality[(d)]:** potentially serious limitations

Abbreviations: CCA: cost–consequence analysis; 95% CI: 95% confidence interval; ED: emergency department; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years.

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long?

(b) Converted using 2008purchasing power parities.[50]

(c) Directly applicable/Partially applicable/Not applicable.

(d) Minor limitations/Potentially serious limitations/Very serious limitations.

Study	**Karnon 2008[16,29]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Decision tree model **Approach to analysis:** A decision tree model developed to describe series of error points and subsequent error detection points in pathways through the medication process in a generic secondary care setting. Errors were	**Population:** Inpatients at 400 beds acute hospital (average hospital size) with around 14 wards and approximately 162,000 prescriptions per year. **Cohort settings:** Start age: NR Male: NR **Intervention 1:** No ward based pharmacist (a pharmacist covers 2 wards of about 30 patients	**Total costs (per hospital over 5 years):** Intervention 1:£ 0.6 million Intervention 2: £0.42 million Incremental (2−1):£ 0.18 million (95% CI: NR; p=NR) **Currency & cost year:** 2006 UK pounds **Cost components incorporated:** Monetary values were assigned to interventions,	**QALYs (per hospital over 5 years):** Intervention 1:NR Intervention 2: NR Incremental (2−1): 285 (95% CI: NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £631.57 per QALY gained[(b)] 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Net monetary benefit over 5 years:** **Minimum intervention cost scenario:** £27.256 million (pa) (95% CI: £5.673 to £69.520 million; p=NR) **Maximum intervention cost scenario:** £26.509 million (pa) (95% CI: £4.925 to £68.772 million; p=NR)

classified as significant, serious, life-threatening or fatal. The effectiveness of potential interventions was estimated by describing their impact on error incidence and detection rates which alters the estimated frequency of errors and preventable adverse events (pADEs) and consequently their associated costs and health effects. **Perspective:** UK NHS **Time horizon:** 5 years **Treatment effect duration[(a)(a)]:** 5 years **Discounting:** Costs: NR ; Outcomes: NR	over a morning to provide basic level of pharmaceutical care and in the afternoons they have departmental commitments) **Intervention 2:** Ward based senior pharmacist (grade 7/8a) attends rounds with residents, nurses, attending staff each morning, is present in the ward for consultation and assistance to nursing staff during the rest of the morning and is available on call as necessary during the rest of the day.	efficiency savings, treatment and health effects of pADEs. Costs included: pharmacist time, length of stay, litigation costs		**Analysis of uncertainty:** The analysis was run using the lower and upper estimates of the intervention cost, which were calculated assuming an average of 2.5 and 1.5 wards per morning per pharmacist in the intervention 1 scenario. The authors presented another analysis including the cost of treating pADEs only but not the monetary valuation of the health outcomes (QALYs), which showed that the ward-based pharmacist intervention had small expected negative NMB for both the minimum and maximum intervention cost scenario.
Data sources				
Health outcomes: Baseline event data were subjectively defined by the authors based on evidence from the literature and qualitative findings from an expert elicitation workshop. Effectiveness data are based on a review of the literature; however, this hasn't been described in the current paper in detail but in a separate project report.[30] **Quality-of-life weights:** estimates of utility decrements were based on discussions within the research team. **Cost sources:** Cost of pharmacist time was taken from national sources, while estimates of other resource use and costs were based on published literature. NHS litigation costs were also included and based on estimates from the NHS litigation authority database.				
Comments				
Source of funding: governmental funding (Department of Health). **Applicability and limitations:** Some uncertainty regarding the applicability of resource use and costs from the literature, which were converted to 2006 UK pounds and adjusted for inflation. No discounting was applied despite using a 5-year time horizon. Utility decrements due to medication errors are based on estimates reached at through discussion within the research team and not based on data collected from patients. The model has a relatively short time horizon and may not capture all the relevant costs and outcomes, given the potential for preventing fatal medication errors. The health outcomes assessed included only QALY gains from prevention of medication errors. The authors reported that the estimates of baseline and relative				

effectiveness are "subjectively defined by the authors based on evidence from the literature and qualitative findings from an expert elicitation workshop involving mixture of human factors experts and health professionals to estimate individual error incidence and detection rates", however no detail is given regarding how the evidence has been identified or reviewed. Costs relating to the time of other health care professionals, which might be affected by more pharmacist involvement, have not been included.

Overall applicability[(c)]: partially applicable **Overall quality[(d)]:** potentially serious limitations

Abbreviations: 95% CI: 95% confidence interval; CUA: cost–utility analysis; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long.

(b) Calculated by NGC

(c) Directly applicable/Partially applicable/Not applicable

(d) Minor limitations/Potentially serious limitations/Very serious limitations

Study	**Klopotowska 2010[32]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: prescribing errors, patient harm) **Study design:** before and after comparative interventional study **Approach to analysis:** Data were collected during a baseline period, with no ICU hospital pharmacist intervention, on the incidence of prescribing errors, rate of consensus, number of preventable adverse drug events (pADEs); defined as prescribing errors that	**Population:** Patients in an adult surgical and medical 28-bed ICU of the academic Medical Centre, a 1,002-bed (tertiary care) academic hospital in Amsterdam, the Netherlands. **Cohort settings: (n=1,173)** Mean age: Intervention 1:63.2 years Intervention 2: 61.3 years Male: Intervention 1: 36.5% Intervention 2: 35.5%	**Total costs (mean per patient)[(a)]:** Intervention 1: assumed zero Intervention 2: -£108 Incremental (2−1): -£108 (95% CI: NR; p=NR) **Currency & cost year:** 2007 euros (presented here as 2007 UK pounds [(b)]) **Cost components incorporated:** Pharmacists' time Physicians' time pADEs	**Incidence of prescribing errors (mean per patient)** Intervention 1: 0.57 Intervention 2: 0.19 Incremental (2−1): -0.38 (95% CI: -0.27 to -0.5; p<0.001) **Incidence of prescribing errors that resulted in patient harm[(c)] (pADEs) (mean per patient)** Intervention 1: 0.012 Intervention 2: 0.003 Incremental (2−1): -0.009 (95% CI: NR; p=0.25) **Incidence of potentially**	**ICER (Intervention 2 versus Intervention 1):** n/a **Analysis of uncertainty:** No sensitivity analysis reported A subgroup analysis was conducted to compare the results during the first half of the intervention period (4 months) with the second half, to account for the learning curve. The analysis showed significant difference in outcomes between the 2 periods, with the second period showing better outcomes

resulted in patient harm. These baseline data were collected for 3 weeks. The same data were collected during the intervention period. Cost of delivering the intervention was calculated as the cost of the pharmacist time. The cost of doctors' time was also calculated. Unpaired student t-test was used to compare costs. **Perspective:** Dutch healthcare **Follow-up:** ICU stay. **Treatment effect duration:** same as follow-up. **Discounting:** Not discounted.	**Intervention 1: (n=115)** Standard pharmacy services provided by the hospital pharmacy department including on-call availability of a hospital pharmacist or hospital pharmacy resident for consultations and therapeutic drug monitoring. Pharmacy technicians prepared ready-to-use parenteral medication at an ICU based satellite pharmacy. The prepared medications were reviewed twice a day by a hospital pharmacist at the central pharmacy department. **Intervention 2: (n=1,058)** Two hospital pharmacists with more than 10 years hospital practice experience trained in the ICU for 4 weeks prior to starting were present on the ICU daily for 8 months, reviewing medication orders and recording prescribing issues. These issues were then discussed with ICU physician during the multidisciplinary patient review meeting.		**harmful pADEs (mean per patient):** Intervention 1: 0.16 Intervention 2: 0.048 Incremental (2−1): -0.552 (95% CI: -0.051 to -0.174; p<0.001) **Incidence of prescribing errors that did not result in harm (mean per patient):** Intervention 1: 0.399 Intervention 2: 0.136 Incremental (2−1): -0.263 (95% CI: -0.166 to -0.359; p<0.001)	
Data sources				
Health outcomes: data on prescribing errors and patient harm (pADEs) were collected during the baseline observation period and the intervention period and				

compared. Cost of pharmacist and physicians' time were calculates well as the cost of the recorded pADEs. **Quality-of-life weights:** n/a. **Cost sources:** ICU pharmacists' and physicians' time costs were based on national unit costs. Potential savings from the pADEs were calculated using estimates from Bates 1997[6] in 1997 US dollars converted to 2007 euros.

Comments

Source of funding: the Netherlands Organization for Health Research and Development (ZonMW), The Hague. **Applicability and limitations:** QALYs were not used as an outcome measure and only costs and cost savings were included as outcomes. Some uncertainty regarding the applicability of resource use and costs from the Netherland (2007) to current NHS context. The intervention is delivered by senior clinical pharmacists but with limited ICU experience, which may not be the same as in NHS hospitals. The study is a cost-consequences analysis with only patient harm as a health outcome. The costs included were limited to staff time and potential saving from pADEs, while the cost of hospital stay and medication were not included. The study follow-up is short (ICU stay) and may not capture all relevant costs and outcomes. No sensitivity analysis is reported.

Overall applicability[(c)]: partially applicable **Overall quality[(d)]:** potentially serious limitations

Abbreviations: CCA: cost–consequence analysis; 95% CI: 95% confidence interval; ICER: incremental cost-effectiveness ratio; ICU: intensive care unit; n/a: not applicable; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Calculated by NGC

(b) Converted using 2007purchasing power parities.[50]

(c) Defined as temporary or permanent impairment of the physical, emotional or psychological function or structure of the body and/or pain requiring intervention resulting from this impairment.

(d) Directly applicable / Partially applicable / Not applicable

(e) Minor limitations / Potentially serious limitations / Very serious limitations