PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2017; **26**: 481–497
Published online 13 March 2017 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.4188

ORIGINAL REPORT

# Economic impact of medication error: a systematic review†

Elaine K. Walsh[1]*, Christina Raae Hansen[2,3], Laura J. Sahm[2,4], Patricia M. Kearney[5], Edel Doherty[6] and Colin P. Bradley[1]

[1] *Department of General Practice, University College Cork, Cork, Ireland*
[2] *School of Pharmacy, University College Cork, Cork, Ireland*
[3] *Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark*
[4] *Mercy University Hospital, Cork, Ireland*
[5] *Department of Epidemiology and Public Health University College Cork, Cork, Ireland*
[6] *Department of Economics, National University of Ireland Galway, Galway, Ireland*

## ABSTRACT

**Purpose** Medication error is a significant source of morbidity and mortality among patients. Clinical and cost-effectiveness evidence are required for the implementation of quality of care interventions. Reduction of error-related cost is a key potential benefit of interventions addressing medication error. The aim of this review was to describe and quantify the economic burden associated with medication error.
**Methods** PubMed, Cochrane, Embase, CINAHL, EconLit, ABI/INFORM, Business Source Complete were searched. Studies published 2004–2016 assessing the economic impact of medication error were included. Cost values were expressed in Euro 2015. A narrative synthesis was performed.
**Results** A total of 4572 articles were identified from database searching, and 16 were included in the review. One study met all applicable quality criteria. Fifteen studies expressed economic impact in monetary terms. Mean cost per error per study ranged from €2.58 to €111 727.08. Healthcare costs were used to measure economic impact in 15 of the included studies with one study measuring litigation costs. Four studies included costs incurred in primary care with the remaining 12 measuring hospital costs. Five studies looked at general medication error in a general population with 11 studies reporting the economic impact of an individual type of medication error or error within a specific patient population.
**Conclusions** Considerable variability existed between studies in terms of financial cost, patients, settings and errors included. Many were of poor quality. Assessment of economic impact was conducted predominantly in the hospital setting with little assessment of primary care impact. Limited parameters were used to establish economic impact. Copyright © 2017 John Wiley & Sons, Ltd.

KEY WORDS—economic; cost; medication error

*Received 16 May 2016; Revised 15 December 2016; Accepted 30 January 2017*

## INTRODUCTION

Medication error is a significant source of preventable morbidity and mortality among patients.[1] The medication use process involves drug prescription, preparation, dispensing and administration. Definitions of medication error vary in the literature,[2] and errors may occur at any point in the medication use process and may involve physicians, pharmacists and nurses in primary, secondary and tertiary care settings. Additionally, patients may not take medications as prescribed, a phenomenon referred to as medication non-adherence.[3] Medication error may result in preventable adverse drug events (pADEs) resulting in patient harm and considerable financial cost.[1] Not all medication errors result in patient harm but may however be associated with other negative consequences such as inefficiency and inappropriate use of resources, contributing to economic burden.[4] Medication safety is a key component in quality of patient care and developing strategies to reduce medication error is currently an international priority.[5–7]

Interventions to reduce medication error may target health-care professionals inclusive of physicians, pharmacists and nurses and additionally may target patient-non adherence. Increasingly, interventions to improve quality of care in the health care sector are required

*Correspondence to: E. Walsh, Department of General Practice, Western Gateway Building, University College Cork, Western Rd, Cork, Ireland. Email: elaine.walsh@ucc.ie

†This work was presented at the PRIMM conference in London, UK January 29-01-16 and at the SPHERE conference in Dublin, Ireland in 29-02-16.

to demonstrate effectiveness from both a clinical and cost perspective. When conducting an economic evaluation of a quality improvement intervention the identification, measurement and valuation of both the relevant costs and the relevant benefits is required.[8] Because of the complex nature of the medication error process; interventions to reduce medication error are often multifaceted and resource intensive.[9,10] In the case of interventions to reduce medication error, reduction of the cost due to error is a key potential benefit. Hence, an accurate estimate of the economic burden associated with medication error is necessary to inform the successful development and implementation of interventions focussing on its reduction.

The aim of this review is to establish the economic impact of errors associated with the prescription, preparation, dispensing and administration of medication. Additionally, the review will identify methods and parameters used when calculating the cost of medication error and also identify the types of medication error that result in economic burden. It will provide evidence for healthcare decision makers regarding the costs associated with medication error and will also highlight areas requiring further study for practitioners and policymakers.

## METHODS

### *Search strategy*

Searches were conducted of the following databases: PubMed, Cochrane, Embase, CINAHL, EconLit, ABI/INFORM and Business Source Complete in June 2015 for publications dating back to January 2004. The search was updated in April 2016. The search strategy was developed by the primary author in association with a medical librarian. A PubMed Strategy was developed and appropriate Medical Subject Headings terminology was utilised. The following search terms were employed: (Cost OR Cost analysis OR Econ*) combined with (Medication error OR Inappropriate Prescribing OR 'Inappropriate Medication' OR Preventable adverse drug event* OR Preventable adverse drug reaction* OR Prescribing error* OR OR Transcription Error* OR Medication Discrep* OR Medication omission*). Similar search strategies with Medical Subject Headings terms mapped to appropriate keywords were used for additional databases. (See Appendix 1 for the full search strategy). Search results from multiple databases were transferred to a reference manager-End Note. Title review was conducted by the primary author (E. W.). Studies that clearly did not meet eligibility criteria were excluded. Abstract review was performed by the primary author, and studies that did not meet the inclusion criteria were excluded. Full text review was performed by E. W. and secondary author (C. H.). Where disagreement arose between the primary and secondary authors regarding study inclusion a third author (L. S.) was involved, and a consensus was reached.

### *Review criteria and data extraction*

The review was conducted according to the PRISMA guidelines,[11] and the protocol for the review was registered with PROSPERO. (See Appendix 4) Studies were required to meet the criteria specified in Table 1

Medication error was defined as 'an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient' as per the European Medicines Agency (EMA) Good Practice Guide on recording, coding, reporting and assessment of medication errors.[12] Failure in the drug treatment process was defined as human or process mediated failures rather than lack of efficacy of the drug and included errors of omission. Four categories of medication errors were included in the review:

1 Medication errors with harm
2 Medication errors without harm
3 Intercepted medication errors
4 Potential medication errors

Table 1. Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|---|---|
| Published peer reviewed full text articles | Non-peer reviewed literature e.g. technical reports, Letters to the editor, newspaper articles Grey literature |
| Studies published in the English language | |
| Studies focussing on errors in the prescribing, transcribing, dispensing or administration of medication | Studies focussing on the prescribing of potentially inappropriate medications, non-compliance or non-adherence to medication. Studies focussing on non-preventable adverse drug reactions Studies focussing on errors in drug manufacturing |
| Studies focussing on the economic burden associated with medication error | Economic evaluations of interventions to reduce error Studies evaluating non-medication related medical error Studies comparing the costs of the adverse drug reactions of two or more medications |



DOI: 10.1002/pds

The definition does not include adverse drug events and adverse drug reactions that are non-preventable. Additionally, the prescribing of potentially inappropriate medications and non-compliance/non-adherence to medication were not included in the definition of medication error used in this review.

The references of eligible studies and previously published systematic reviews were hand searched to identify any additional studies pertaining to the economic impact of medication error not captured by database searching. Studies which met the inclusion criteria were reviewed and data extracted by the primary and secondary authors (E. W. and C. H.) using a data collection form. (See Appendix 2)

Information collected included details of authors, type of medication error, study setting, study population, study sample size, economic method, outcome measures and results.

*Quality assessment:*

Study quality assessment was assessed by the six parameters described by Cooper *et al.*[13]:

1 Viewpoint/perspective (e.g. patient/health service) of the analysis clearly stated and justified.
2 Study population clearly stated.
3 All relevant medical and/or non-medical costs included and their sources clearly stated.
4 All costs adjusted for differential timing, where appropriate: discounting applied to costs if a study was conducted over >1 year.
5 Incremental/attributable costs calculated: calculation of difference in costs incurred by the study population and a non-exposed population.
6 Sensitivity analysis performed to address uncertainties or methodological controversy.

An additional seventh parameter was added to assess study quality based on the EMA guidance on the appropriate recording and reporting of medication errors[12]:

7 Clear statement if reported costs pertained to an actual or potential error and if the error was associated with harm

*Data synthesis*

A narrative synthesis was performed using the approach described by Popay *et al.*[14]:

1 Results were tabulated, and a preliminary synthesis performed.
2 Data was transformed, and a common rubric established so as to express the results in a common numerical value. Costs in all studies were expressed in Euro 2015 values, and a cost value per medication error was calculated where data was available.
3 Relationships within and between studies were explored.
4 Robustness of the synthesis was assessed.

Subgroup analysis was stated a priori and was conducted by age (> or <65 yrs) and type of medication error.

In order to adjust for the inflation rate over time cost in each of the studies was inflated to 2015 values using the consumer price index for medical and non-medical resources for each individual country.[15] Each value was then converted to Euro using the exchange rate from November 2015. Where year of currency was absent from the study, the year of publication was used.

## RESULTS

Following elimination of duplicates, the search strategy yielded 4572 titles for review. Reasons for exclusion are outlined in Figure 1. Disagreement arose regarding inclusion of one study between the primary and secondary authors (E. W. and C. H.). The opinion of a third author (L. S.) was sought, and a consensus was reached.

A summary of the 16 studies which met inclusion criteria is listed in Table 2. The studies were conducted in the USA ($n$ = 7), Europe ($n$ = 5), Asia ($n$ = 3) and South America ($n$ = 1).

*Quality assessment*

Table 3 outlines the parameters used to assess study quality. The viewpoint adopted was explicitly stated in only four of the studies[16–19] but could be implied by the cost data used in all cases. The study population was provided by all studies, as was a clear description of the costs used in the analysis. Discounting was applicable to four of the included studies but was not conducted in any of the four studies. All other studies estimated costs over a 1-year period or less. Less than half ($n$ = 7) of the studies measured incremental costs with a sensitivity analysis being conducted in only two of the included studies. Nine of the included studies reported medication errors as per the EMA guidance.[12] Only one of the included studies fulfilled all applicable quality criteria.[18]

*Study design and population:*

Nine studies were cross-sectional in design,[16,19,25–31] four of case–control design[17,18,20,21] and three comparative studies of modified case–control design.[22–24]



DOI: 10.1002/pds

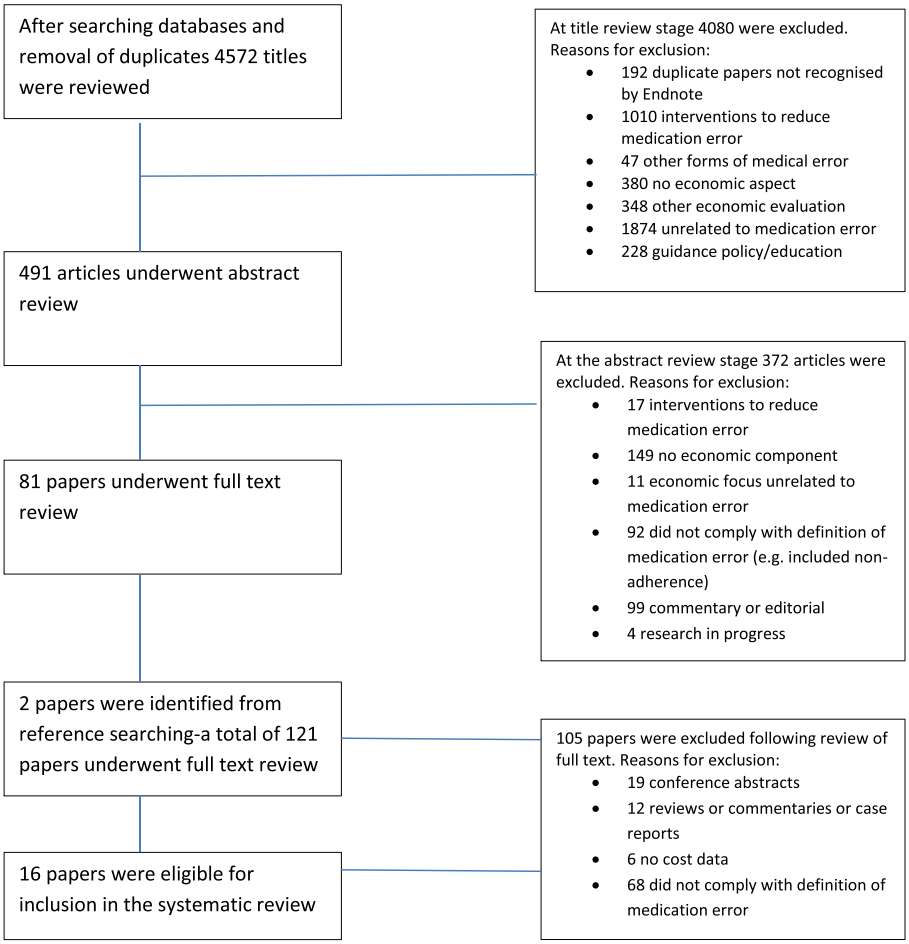


Figure 1. Reasons for exclusion of studies. [Color figure can be viewed at wileyonlinelibrary.com]

Studies were conducted primarily among hospital inpatients ($n$ = 12)[17–20,22,24–30] with four studies including patients in primary care[16,21,23,31]; two of which assessed economic impact exclusively among primary care patients.[21,31]

The majority of studies ($n$ = 15) examined economic impact of error in an adult study population.[16–30] Of these 15 studies, two examined economic impact in elderly patients (>65 years). [21,25] Field *et al.* assessed economic impact of medication error solely among elderly patients[21] whereas Hoonhout *et al.* completed a separate assessment of economic impact of medication error in patients <65 years and >65 years, respectively.[25] A further eight of the included studies examined economic impact within specific patient groups namely: patients experiencing drug errors during anaesthesia,[30] hospital inpatients on a nephrology ward,[28] patients with HIV,[23] hospital inpatients in receipt of an injectable medication,[18] hospital inpatients in receipt of intravenous patient controlled analgesia,[19] hospital inpatients in receipt of anti-neoplastic agents,[29] patients prescribed oxycodone[27] and hospital inpatient prescribed inhaled medication.[26] A single study described economic impact in a paediatric population (children 0–18 months).[31]

### *Methods used to establish economic impact:*

Of the included studies, 12 measured actual costs pertaining to medication errors to which the study population was exposed.[17,18,20–24,26–28,30,31] Three studies measured potential costs because of medication error as decided by an expert panel.[19,25,29] Three studies used economic modelling.[16,18,20] The first of these calculated costs using economic methods inclusive of variables such as age, sex and co-morbidity.[20] The second combined the costs of errors detected among the study population with the probability of the error occurring[18] and the third combined the cost of errors detected with the probability of the outcome measure occurring.[16]



DOI: 10.1002/pds

Table 2. Summary of studies included in the review

| First author Year | Title | Study design Methods used to identify medication errors | Study population Study setting | Sample size patients | Sample size errors | Type of medication error. EMA Classification* | Economic method | Outcome measure | Results |
|---|---|---|---|---|---|---|---|---|---|
| **Studies reporting the economic impact of general medication error** | | | | | | | | | |
| Choi[20] 2016 | Incidence and treatment costs attributable to medication errors in hospitalized patient | Case control: Retrospective review of voluntary error reports completed by physicians, pharmacists and nurse | Hospital in patients (secondary/tertiary care), USA | 57 554 | 470 | Error of ordering, transcription, dispensing and administration. Errors with harm and without harm | Measuring of direct costs via recycled prediction and Blinder-Oaxaca methods | Additional hospital treatment costs incurred by patients experiencing a medication error | 470 errors costed (with and without harm): Recycled prediction method: €8278.94 Blinder-Oaxaca decomposition method: €7851.87 |
| Samp[16] 2014 | Economic evaluation of the impact of medication errors reported by US clinical pharmacists | Cross sectional: Retrospective review of errors observed by clinical pharmacists in practice | Patients in primary/ secondary/ tertiary care, USA | Not stated | 779 | pADE **(Any preventable event that may cause or lead to inappropriate medication use or patient harm) Errors with harm Errors without harm | Measuring of direct costs, modelling via a decision tree | Costs due to error: -monitoring (costs of monitoring tests) -medication regimen change (pharmacists dispensing fee)- permanent harm to patient (equated to harm resulting from stroke) combined with the probability of the outcome occurring | Cost per error (with and without harm): **1** €85.82 (base case) **2**€ 86.58 USD (Monte Carlo simulation) |
| Hughes[22] 2012 | The cost of adverse drug events in community hospitals | Comparative study (Case V total study population comparison): Retrospective review of patient records to identify preventable adverse drug events | Hospital inpatients (secondary/ tertiary care,) The Netherlands | 2100 | 190 | pADE** (an error in the process of ordering, delivering or administering a drug resulting in patient harm) Errors with harm | Measuring of direct costs, opportunity and capital costs | Additional costs incurred by cases: **1** Hospitalisation cost (Operating cost, capital cost) **2** Length of hospital stay Unadjusted Adjusted for age, sex, illness severity, individual hospital | Cost per error (with harm): 1 Increase in average hospitalisation cost €6432.16/ €4659.76 (mean/median) 2 Increase in average length of stay unadjusted 4.64/4.0 days (mean/median) adjusted 3.37/ 2.36 days (mean/median |
| Hoonhout[25] 2010 | Nature, occurrence and consequences of medication-related adverse events during | Cross sectional: Retrospective review of patient records by a nurse and 2 physician reviewers | Adult inpatients in community hospitals | 7889 | 45 | pADE** (harm caused by medication due to not following the | Measuring of direct costs | Potential clinical costs as decided by an expert panel: | Cost per error (with harm): **1** Excess length of stay 6.9 days |

(*Continues*)


DOI: 10.1002/pds

Table 2. (Continued)

| First author Year | Title | Study design Methods used to identify medication errors | Study population Study setting | Sample size patients | Sample size errors | Type of medication error. EMA Classification* | Economic method | Outcome measure | Results |
|---|---|---|---|---|---|---|---|---|---|
| | hospitalisation. A retrospective chart review in the Netherlands | to identify preventable adverse drug events | (secondary care), USA | | | professional standard or poor organisation of care)<br>Errors with harm | (potential costs) | **1** Excess length of stay<br>**2** Excess hospitalization costs | (95% CI 2.2, 7.8)<br>**2** Excess hospitalisation costs €3456.38 (95% CI €1172.96, €6105.14) |
| Pinilla[17] 2006 | Case control analysis of the financial cost of medication errors in hospitalised patients | Case control: Retrospective review of voluntary error reports completed by physicians, nurses and pharmacists | Adult inpatients in private hospital (tertiary care), Spain | 172 (86 per arm) | 86 | Errors of validation, dispensing, administration, inattention, illegibility, labelling, packaging, lack of recording, misinterpretation<br>Errors with harm<br>Errors without harm | Measuring of direct costs | Only errors reaching the patient were costed<br>Additional costs incurred by patients:<br>**1** Hospital costs (cost of stay, drugs, radiology. Healthcare material)<br>**2** Length of stay | 63 errors costed (with and without harm):<br>**1** €2184.93/ €1510.15(mean/ median) greater hospital costs<br>**2** 303 days of additional hospitalisation |
| **Studies reporting the economic impact of an individual type of medication error or error within a specific population** | | | | | | | | | |
| Zaidi[26] 2015 | Quantifying and reducing inhaler prescription errors in secondary care | Cross sectional: Review of incorrect prescriptions by pharmacists | Hospital inpatients prescribed an inhaler (secondary/ tertiary care), UK | Not stated | 61 | Prescription error (incorrect device, strength or drug)<br>Intercepted medication errors | Measuring of direct cost | Cost of erroneous medication | Cost per error (intercepted error):<br>€67.93 (mean) |
| Zahari[27] 2014 | Duplication of oxycodone prescriptions at pharmacy department, Hospital University Sains Malaysia (HUSM) | Cross sectional: Retrospective, prescription review | Hospital inpatients Prescribed oxycodone 14–90 years (secondary/ tertiary care), Malaysia | 212 | 103 | Prescription error (duplication)<br>EMA Classification unknown | Measuring of direct cost | Cost of medication | Total cost(EMA Classification unknown)<br>€3308.80 |
| Gharekhani[28] 2014 | Frequency, types and direct related costs of medication errors in an academic nephrology ward in Iran | Cross sectional: Prospective, detection of medication errors by clinical pharmacists on a nephrology ward | Adult inpatients prescribed 1 or more medications in a hospital nephrology ward (tertiary care), Iran | 350 | 1372 | Prescription errors, transcription errors, drug administration errors<br>Intercepted medication errors | Measuring of direct costs | Medication cost | 1372 errors costed (intercepted):<br>€7683.20 |
| Al-lela[31] 2012 | Estimation of immunization providers' activities cost, medication cost and immunization dose errors | Cross sectional: Retrospective review of immunisation records | Children 0-18 months in Public Health Clinic (primary care), Iraq | 528 | 483 | Unnecessary (early) and invalid (extra) immunisation dose<br>EMA classification unknown | Measuring of direct costs | **1** Cost of vaccine<br>**2** Cost of service (time and average salary of administrator, | 483 errors costed (EMA classification unknown):<br>288 Early vaccine doses: |

(*Continues*)

Table 2. (Continued)

| First author Year | Title | Study design Methods used to identify medication errors | Study population Study setting | Sample size patients | Sample size errors | Type of medication error. EMA Classification* | Economic method | Outcome measure | Results |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | physician and nurse) | Vaccine cost €244.51 Service Cost €497.14 195 Extra doses: Vaccine Cost € 176.52 Service Cost €325.30 Total cost: €1243.47 |
| Lahue[18] 2012 | National burden of preventable adverse drug events associated with inpatient injectable mediations: healthcare and professional liability costs | Case control: Retrospective review of medication error reporting system database for preventable adverse drug reactions with classification by 2 independent physicians | Hospital inpatients in receipt of an injectable medication (secondary/ tertiary care), USA | 37 513 | 303 | pADE** (an injury occurring as a result of an error in the medication use process) Errors with harm | Measuring of direct costs, modelling | Additional costs incurred by cases: -Inpatient services -Post discharge physician services combined with the probability of a pADE occurring | Cost of errors (with harm): 1 Cost of pADEs per hospital admission: €2879.03 (95% CI €2507.54, €3343.39) 2 Annual additional cost of pADEs in USA: €3.65 billion (95% CI €2.51, €4.73) 3 Average annual inpatient cost of pADEs per hospital: €576,420 |
| Ranchon[29] 2011 | Chemotherapeutic errors in hospitalised cancer patients: attributable damage and extra costs | Cross sectional: Prospective, observation of routine practice with errors being detected by pharmacists, pharmacy technicians, physicians, nurses, | Patients receiving anti-neoplastic agents in inpatient and day care units (secondary/ tertiary care), France | 341 | 449 | Errors of prescription, preparation, administration Intercepted medication errors | Measuring of direct costs (potential costs) | Potential clinical costs as decided by an expert panel 1 Cost of new potential hospitalisation 2 Cost of potential prolongation of hospitalisation 3 Cost of medication 4 Length of stay | 449 errors costed (intercepted errors): 1 Cost new potential hospitalisation €9678.87 2 Cost potential prolongation of hospitalisation €65961.38 3. Medication cost €25842.29 Total 1–3: 101482.54 |

(*Continues*)


DOI: 10.1002/pds

Table 2. (Continued)

| First author Year | Title | Study design Methods used to identify medication errors | Study population Study setting | Sample size patients | Sample size errors | Type of medication error. EMA Classification* | Economic method | Outcome measure | Results |
|---|---|---|---|---|---|---|---|---|---|
| Hellinger[23] 2010 | The cost and incidence of prescribing errors among privately insured HIV patients | Comparative (exposed V unexposed): Retrospective review of health insurance database to detect prescription of anti-retroviral drugs and interacting drugs | Patients with HIV with private health insurance in primary/ secondary/tertiary care, USA | 12 226 | 644 | Drug–drug interaction Unknown EMA classification | Measuring of direct costs | Annual healthcare utilisation cost incurred by those exposed to error: -Inpatient: cost of stay, laboratory, physician fee -Outpatient: all services and physicians fees in outpatient and emergency department facilities | **4** 216 additional hospital days Additional annual cost(EMA classification unknown): €4337.52 |
| Cranshaw[30] 2009 | Litigation related to drug errors in anaesthesia: an analysis of claims against the NHS in England | Cross sectional: Retrospective review of National Health Service (NHS) litigation authority database of clinical claims made against the NHS from patients alleging harm from drug errors in anaesthesia | Patients alleging harm from drug errors in anaesthesia in hospital (secondary/ tertiary care), UK | 1067 | 62 | Drug administration error (wrong drug, dose, order, route or drug omission) Errors with harm | Measuring of direct costs | Cost of clinical claims made against the NHS by patients | 62 errors costed (with harm): €6 927 078.96 |
| Meissner[19] 2009 | The rate and costs attributable to intravenous patient controlled analgesia (IV PCA***) errors | Cross sectional: Retrospective review of database of medication errors reported on a voluntary basis by nurses and pharmacists | Hospital inpatients in receipt of IV PCA (secondary/ tertiary care), USA | Not stated | 2356 | Errors of communication, name confusion, storage, human factors, systems, ignored contraindications, equipment Errors with harm Errors without harm | Measuring of direct and opportunity costs (potential costs) | Potential clinical costs due to error as decided by an expert panel: Direct costs: additional drug therapy, lab tests, radiology, hospital length of stay, medical supplies, labour-nurse, pharmacist, physician Opportunity costs: missed revenue from the hospital that could have been generated should the error not have occurred have occurred | Cost per error (with and without harm): -Overall: €827.99 (mean) - Communication €1312.58 (mean) -Name confusion €101.31 (mean) -Storage: €262.29 (mean) -Human factor €803.76 (mean) -Systems error: €1004.13(mean) - Contraindicated: €657.41 (mean) |

(*Continues*)

Table 2. (Continued)

| First author Year | Title | Study design Methods used to identify medication errors | Study population Study setting | Sample size patients | Sample size errors | Type of medication error. EMA Classification* | Economic method | Outcome measure | Results |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | -Equipment related €1338.47(mean)<br>-Default: €451.41 (mean)<br>63 errors (with and without harm)<br>**1** €2184.93/ €1510.15 (mean/median) greater hospital costs<br>**2** 303 days of additional hospitalisation |
| Moura[24] 2009 | Drug–drug interactions associated with length of stay and cost of hospitalisation | Comparative study (exposed V unexposed): Retrospective review of hospital pharmacy prescription records for drug interactions | Hospital inpatients >18 yrs, length of stay > 24 hours (secondary /tertiary care), Brazil | 589 | 220 | Drug–drug interaction EMA Classification unknown | Measuring of direct costs | **1** Additional length of hospital stay patients exposed to drug–drug interaction<br>**2** Association of exposure to drug–drug interaction with high cost of hospitalisation | Economic impact (EMA classification unknown):<br>**1** Increased mean length of stay of 7 days<br>**2** Positive association with high cost of hospitalisation (OR 3.1, 95% CI 2.19–4.42) |
| Field[21] 2005 | The costs associated with adverse drug events among older adults in the ambulatory setting | Case control: Retrospective review of ambulatory medical records for preventable adverse drug events by trained clinical pharmacists and classification by a pharmacist and nehprologist | Elderly patients (65 years and over) enrolled in Medicare in ambulatory care: multispecialty group practice (primary care), USA | 2500 (1225 per arm) | 323 | pADE** (Injury resulting from a drug error) Errors with harm | Measuring of direct costs | Additional health service utilization cost incurred by the case group:<br>-Inpatient stay<br>-Emergency Department visit<br>-Outpatient care<br>-Pharmacy (drug cost) | Cost per error (with harm): €1867.08 (95%CI €244.51, €4779.98) |

*European Medicine's Agency (EMA) Classification[12]:
1. Medication errors with harm
2. Medication errors without harm
3. Intercepted medication errors
4. Potential medication errors
**pADE: Preventable Adverse Drug Event
***IV PCA, intravenous patient controlled analgesia.

Table 3. Assessment of study quality

| Study | Viewpoint | Population | Relevant costs | Discounting | Incremental costs | Sensitivity analysis | Costs reported as per EMA* guide |
|---|---|---|---|---|---|---|---|
| Choi[20] | [+] | + | [+] | 0 | + | 0 | [+] |
| Samp[16] | + | + | [+] | N/A | 0 | + | + |
| Hughes[22] | [+] | + | [+] | 0 | [+] | 0 | + |
| Hoonhout[25] | [+] | + | [+] | N/A | 0 | + | + |
| Pinilla[17] | + | + | [+] | N/A | + | 0 | + |
| Zaidi[26] | [+] | + | 0 | N/A | 0 | 0 | [+] |
| Zahari[27] | [+] | + | 0 | N/A | 0 | 0 | 0 |
| Gharekhani[28] | [+] | + | [+] | 0 | 0 | 0 | 0 |
| Al-lela[31] | [+] | + | [+] | N/A | 0 | 0 | 0 |
| Lahue[18] | + | + | [+] | N/A | + | + | + |
| Ranchon[29] | [+] | + | [+] | N/A | 0 | 0 | + |
| Hellinger[23] | [+] | + | [+] | N/A | [+] | 0 | 0 |
| Cranshaw[30] | [+] | + | [+] | N/A | 0 | 0 | + |
| Meissner[19] | + | + | + | 0 | 0 | 0 | + |
| Moura[24] | [+] | + | [+] | N/A | + | 0 | 0 |
| Field[21] | [+] | + | [+] | N/A | + | 0 | + |

Notation based on Rothfuss et al[43]: +, present; [+], partly fulfilled; 0, absent. N/A, non-applicable
*EMA: European Medicines Agency

*Parameters used to establish economic impact:*

*Healthcare costs:* Of the included studies, 15 calculated healthcare costs associated with medication error.[16–29,31] Healthcare costs were comprised of costs associated with hospitalisation, medication, outpatient care and primary care. The parameter used most frequently to establish economic impact of medication error in the included studies was cost of hospitalisation ($n = 11$).[16–25,29]

*Hospitalisation costs:* A total of 11 studies measured hospitalisation costs; all demonstrating increased economic burden associated with medication error.[16–25,29] One of the studies using hospitalisation costs expressed economic impact in terms of increased mean length of stay and a positive association with a high cost of hospitalisation.[24] In the 10 other studies that expressed economic impact in monetary terms; five used health insurance databases[16,18,21,23,29] to calculate hospitalisation costs, three used hospital account information,[17,20,22] one used a combination of information from hospital accounts and health insurance databases[25] and one used a combination of fee schedules and published literature.[19] The definition of hospitalisation costs varied between all 11 studies.

Six of the included studies used hospitalisation costs as an isolated measure of economic impact.[17,19,20,22,24,25] Moura *et al.* assessed economic impact among hospital inpatients in Brazil exposed to prescribing error. Economic impact was not expressed as a monetary figure but rather by mean length of hospital stay and association with cost of hospitalisation in exposed patients.[24] In an American study, Choi *et al.* described excess hospital treatment costs for those experiencing a medication error. No breakdown of costs was given and hospital database information was used to calculate costs.[20] In a study conducted among hospital inpatients in the Netherlands, Hoonhout *et al.* described excess hospitalisation costs among those experiencing a pADE. Costs pertaining to medical and nursing staff, drugs, equipment, inpatient stay and medical procedures were described. A combination of hospital account information and health insurance (Dutch Healthcare authority) information were used in this study.[25] In a Spanish study, Pinilla *et al.* calculated additional hospitalisation costs incurred by patients experiencing medication error. Costs were inclusive of inpatient stay, drugs, scans and healthcare material and hospital account information was used to calculate costs.[17]

Two of the studies using hospitalisation costs as an isolated measure of economic impact used more in-depth costing.[19,22] Hughes *et al.* calculated additional hospitalisation costs incurred by patients experiencing a pADE. The study was conducted among hospital inpatients in the USA, and additional hospital operational and capital costs were calculated using hospital account information.[27] Hospital operating cost was defined as 'the fixed and variable costs for operating a hospital for example, labour and maintenance' and capital costs defined as 'the infrastructural cost of buildings and equipment'.[22] Meissner *et al.* calculated hospitalisation costs among hospital inpatients experiencing medication error relating to intravenous patient controlled analgesia (IV PCA). Costs were



DOI: 10.1002/pds

inclusive of medication, laboratory tests, radiological imaging, inpatient stay, medical supplies, medical pharmacy and nursing staff. Additionally, Meissner *et al.* included missed hospital revenue or opportunity cost defined as 'income that could have been generated should the error not have occurred' when calculating hospitalisation costs. Costs were calculated using fee schedules and published literature.[19]

A further five studies used hospitalisation costs in combination with other measures. Field *et al.* assessed the economic impact of pADEs among elderly ambulatory patients in the USA. Hospitalisation costs in this study were inclusive of inpatient stay and emergency department visits. Additionally, medication costs and outpatient costs inclusive of physician fee, diagnostic tests, laboratory tests, home health visits, medical equipment and ambulance fee were calculated using a health insurance (Medicare) database.[21] Hellinger *et al.* assessed the economic impact of prescribing error among patients with HIV in the USA. Hospitalisation costs inclusive of inpatient stay, laboratory and physician fee were calculated as were additional outpatient costs inclusive of all services and physician fees in outpatient and emergency departments using health insurance (Marketscan) database information.[23] Lahue *et al.* described economic impact associated with pADEs among hospital inpatients in the USA in receipt of an injectable medication. Hospitalisation costs defined as inpatient services were calculated with additional costing of post discharge physician services using health insurance (Medicare) cost.[18] Ranchon *et al.* calculated hospitalisation costs inclusive of inpatient stay in addition to medication costs in hospital inpatients in France receiving anti-neoplastic agents who were exposed to medication error. Cost information was obtained from the French health insurance system.[29] Samp *et al.* assessed economic impact in patients experiencing a pADE by using three parameters: (1) hospitalisation costs represented by inpatient monitoring costs, (2) cost of changes in medication defined as a pharmacists dispensing fee and (3) costs of permanent harm to a patient defined as the cost of a stroke. Cost information was obtained from health insurance database (Medicare) information and from the literature.[16]

*Medication costs:* Cost of medication was used as a measure of economic impact in eight of the included studies. All eight studies demonstrated an increase in medication costs because of medication error. Methods to determine the cost of medication varied between studies, and in three of the studies, it was not explicitly stated how cost of medication error was calculated.

Three studies used medication cost as the sole measure of economic impact.[26–28] Gharekhani *et al.* calculated the economic impact of medication error among patients on a nephrology ward in Iran by calculating the cost paid by the patient or the patient's insurance agency for erroneous medications and the equipment required for medication administration such as syringes or infusion sets.[28] Zahari *et al.* calculated the cost of medication error because of prescription duplication and defined cost of medication broadly as 'current drug price'.[27] Zaidi *et al.* calculated the cost of an incorrectly prescribed inhaler using the hospital drug formulary.[26]

Medication cost was used to measure economic impact in combination with other parameters in six other studies.[17,19,21,25,29,31] Al-lela *et al.* reported the cost of erroneous childhood vaccines and used medication cost in combination with immunisation service cost. Medication cost was calculated as vaccine cost obtained from the Department of Health.[31] Field *et al.* used hospitalisation and medication costs in their analysis. Medication costs were defined as 'the average wholesale cost on the day they were dispensed'.[21] Hoonhout *et al.* included medication costs as a subgroup of hospitalisation costs. Medication costs were obtained from 'Dutch guideline prices' for hospitals.[25] Meissner *et al.* also included medication costs within hospitalisation costs. The method of establishing costs specific to medication is not explicitly stated.[19] Pinilla *et al.* also included medication costs within hospitalisation costs. Overall costs were derived from the hospital accounting system but how costs specific to medication were calculated was not specifically stated.[17] Ranchon *et al.* used medication cost in combination with hospitalisation cost. Medication cost pertained to cost of anti-neoplastic agents. It was implied but not explicitly stated that medication cost was derived from French public health insurance data.[29]

Costs for particular class of medication were provided in three of the included studies namely vaccines, inhaled medications and oxycodone.[26,27,31] No other study specified the type of medication being costed.

*Primary care costs:* Direct costs specific to primary care were calculated in two studies. Al-lela *et al.* costed the time of primary care physicians, nurses and administrators in providing erroneous childhood immunisations in public health clinics in Iraq. Salary information was obtained from the Department of



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Health in Iraq.[31] The errors identified occurred in primary care, and the subsequent cost consequences were costs incurred in primary care. As previously described, Field *et al.* included physician fee, diagnostic tests, lab tests, home health visits, medical equipment and ambulance costs in their analysis of the economic impact of pADEs among ambulatory elderly patients in the USA. It was unclear if the errors identified occurred in primary care or in the hospital setting. Separate primary care costs were not available in this study r as the economic impact reported was a combination of both hospital and primary care costs.[21]

*Outpatient care costs:* Direct costs pertaining to outpatient care were calculated in three studies. All three studies used health insurance database information when calculating costs. Field *et al.* included costs pertaining to physician fee, diagnostic tests, laboratory tests and medical equipment.[21] Hellinger *et al.* calculated costs pertaining to services and physicians fees in outpatient facilities but did not provide a breakdown of what the services included.[23] Lahue *et al.* calculated costs pertaining to post discharge physician services but did not specify what the services included.[18]

*Non-healthcare costs:* One of the included studies calculated costs that were not related to the provision of healthcare but rather to health-professional litigation costs associated with medication error.[30]

*Litigation costs:* Litigation costs, defined as the cost of clinical claims made against the National Health Service (NHS) in the UK regarding medication errors during anaesthesia, were used in a single study and were used as an isolated measure of economic impact. Cost information was obtained from the NHS litigation authority database.[30]

### *Economic impact of medication error:*

Thirteen of the included studies expressed economic impact in monetary terms with one study[24] using length of hospital stay as the primary outcome measure. The economic impact of medication error calculated by the different studies varied considerably.

Five of the included studies reported a cost for medication errors associated with harm,[18,21,22,25,30] four studies reported a combined cost for medication errors associated with harm and without harm,[16,17,19,20] and three studies reported costs for intercepted medication errors.[26,28,29]

Cost per medication error was extracted from 12 of the included studies: see Table 4. A cost per error for general medication error was available in five of the included studies.[16,17,20,22,25] The other seven costs per error pertained to individual types of medication error or medication error within a specific population.[19,21,26,28–31] Mean cost per error per study ranged from €2.58 to €111 727.08. The lowest costs per error were those associated with unnecessary and invalid immunisations in children,[31] and the highest costs per error were litigation costs associated with medication errors during anaesthesia.[30]

### *Types of medication error:*

Cost information on an individual type of medication error was available in 10 of the included studies. Meissner *et al.* reported individual costs for errors of communication, name confusion, storage, human origin, systems, contraindicated medication, equipment and default, respectively.[19] Four further studies reported the economic impact of prescribing error.[23,24,26,27] Five of the included studies reported economic impact of pADEs.[16,18,21,22,25] None of the studies reported errors of omission.

### *Subgroup analysis:*

Three subgroups were identified and are described in Table 5: firstly, the economic impact of prescribing error; secondly, the economic impact of pADEs; and thirdly, the economic impact of medication error in elderly patients. Four of the included studies reported economic impact of prescribing error.[23,24,26,27] Five of the included studies reported economic impact of pADEs.[16,18,21,22,25] Two of the included studies assessed economic impact of medication error in elderly patients (>65 years). [21,25] Study population and measures of economic impact varied between studies.

## DISCUSSION

Studies included in this review assessed the economic impact of medication error in nine different countries over an 11-year period (2004–2015). Considerable variability existed between studies in terms of study design, study population, types of medication error, cost parameters and financial information sources. Hence, meaningful comparison of economic impact between studies was limited. A difference of greater



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Table 4. Reported economic impact and cost per medication error

| Study | Reported economic impact | Cost per error (Euro 2015) |
|---|---|---|
| **General medication error** | | |
| Choi[20] | Cost of 470 medication errors among hospital inpatients: | 17.6/16.7* |
| | | *Figures from 2 different mathematical models* |
| Samp[16] | Cost per pADE | 86.13 |
| Pinilla[17] | For 62 medication errors among hospital inpatients:<br>1. Cost<br>2. Excess length of stay | 2184.93/1510.15 (mean/median) |
| Hoonhout[25] | Per hospital inpatient with pADE:<br>1.Excess length of stay<br>2.Cost per pADE | 3456.38 |
| Hughes[22] | Per community hospital inpatient with pADE:<br>1. Excess length of stay<br>2. Cost per pADE | 6432.16/4659.76 (mean/median) |
| **Individual type of medication error or error within a specific population** | | |
| Al-lela[31] | Cost of 483 erroneous vaccines | 2.58 |
| Gharekhani[28] | Cost of 1372 medication errors on a nephrology ward | 5.6 |
| Zaidi[26] | Cost per erroneous inhaler prescription | 67.93 |
| Ranchon[29] | For 449 errors among patients receiving antineoplastic agents<br>1. Cost<br>2. Excess length of stay | 226.02 |
| Meissner[19] | Cost per medication error among inpatients in receipt of IV patient controlled analgesia | 827.99 |
| Field[21] | Cost per pADE in ambulatory elderly patients | 1867.08 |
| Cranshaw[30] | Cost of 62 drug errors in anaesthesia | 111 727.08 |

pADE = Preventable adverse drug event

Table 5. Subgroups (prescribing error, pADE, medication error in elderly patients)

| Error | Study population | Measure of economic impact | Reported economic impact |
|---|---|---|---|
| **Prescribing error** | | | |
| Drug–drug interaction[23] | Patients with HIV | Additional annual healthcare utilisation cost | €4274.50 |
| Drug–drug interaction[24] | Hospital inpatients | Increased length of hospital stay | 7 days |
| Drug duplicaton[27] | Patients prescribed oxycodone | Total cost of medication | €3244.97 |
| Error of preparation, strength or dose[26] | Patients prescribed inhalers | Cost per medication error | €67.93 |
| **pADE** | | | |
| pADE[22] | Community hospital inpatients | Additional hospitalisation costs per pADE | €6314.35/4574.41 (mean/median) |
| pADE[18] | Hospital inpatients receiving an injectable medication | Additional hospitalisation or post discharge physician services costs of pADEs:<br>1. Per hospital admission<br>2. Annual cost<br>3. Annual inpatient cost | <br>1. €2879.03<br>2. €3.6 billion<br>3. €567 943.22 |
| pADE[16] | Patients in hospital and primary care | Costs of monitoring, medication regimen change, permanent harm to patient per pADE | €84.56 (€85.31 using sensitivity analysis) |
| **pADE > 65 years** | | | |
| pADE[25] | Hospital inpatients | Additional hospitalisation costs per pADE<br>1.Patients <65 years<br>2.Patients > 65 years | <br>€3277.29<br>€3440.88 |
| pADE[21] | Ambulatory patients >65 years | Additional primary and secondary health care utilisation cost per pADE | €2599.96 |

pADE = Preventable adverse drug event

than €100,000 was detected between the lowest and highest costs per individual medication error. Establishing an overall pattern was possible; however, as all of the included studies found medication error to be a significant economic healthcare burden in their respective settings with all studies reporting increased financial costs or length of hospital stay.

Three of the included studies did report a similar cost outcome of additional healthcare utilisation costs per pADE. The highest cost of €6314.35/4574.41 (mean/median) was reported in a study among inpatients in community hospitals in the USA[22] with lower costs of €3440.88 reported in a Dutch study among elderly hospital inpatients[25] and of €2599.96 in an



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American study among elderly ambulatory patients.[21] The study reporting the highest cost per pADE used additional capital and operating costs in their calculation of hospitalisation cost[22] which may account for the difference in cost and may suggest that studies not including such costs are under estimating the true economic impact of medication error. The reason for lower costs in the American study among ambulatory elderly patients compared with the Dutch study among elderly inpatients may be due to the differing countries and healthcare systems. Additionally, the difference may be due to increased morbidity among hospital inpatients compared with ambulatory patients hence contributing to greater costs. As only hospitalisation costs are reported in the Dutch study however, the difference could also suggest that medication errors among patients in primary care are associated with a lower economic burden than those occurring in a hospital setting.

The review identified that the economic impact of medication error has been predominantly explored in the hospital setting and that hospitalisation costs represent the parameter used most frequently to establish the economic impact of medication error. However, variability was detected in both the definitions of hospitalisation costs and the sources of financial information used between studies. Additionally, it was identified that limited parameters have been used to date to establish economic impact of medication error, with included studies using only four parameters in addition to hospitalisation costs namely; medication costs, outpatient costs, primary care costs and litigation costs. Although medication costs were reported for half of the studies, methods to establish medication cost were not explicitly stated nor could they be isolated from overall costs reported in three of the included studies. A minority of studies[18,21,23,31] reported outpatient costs and costs occurring in primary care.

The review established that to date primarily healthcare costs have been used to determine the economic impact of medication error,[16–29,31] with litigation costs being the only additional cost parameter used.[30] Only two of the included studies conducted more in-depth costing of health care related costs through the calculation of hospital operating and capital costs[22] and opportunity cost pertaining to missed hospital revenue.[19] Hence, the true economic burden of medication error may have been underestimated to date.

Economic impact associated with an individual type of medication error could only be extracted in five of the included studies.[19,23,24,26,27] Although four studies reported the economic impact of prescribing error and hence provided information on the economic impact associated with medication error in a particular health care professional group; namely doctors, the outcome measures varied considerably limiting comparison.

### *Comparison with previous reviews*

No previous systematic review has examined the economic impact specifically pertaining to medication error. Lassetter *et al.* conducted a literature review on quality of care and cost issues pertaining to medical error, drug related problems and medication errors in 2003. Although a substantial economic impact was reported, the authors did not distinguish between the economic impact of drug related problems and medication error in their review.[32] Chiatti *et al.* conducted a systematic review on the economic burden of inappropriate prescribing, lack of adherence and compliance and adverse drug events in the elderly. Again although a substantial economic burden was identified, the authors did not separate preventable adverse drug events that are consistent with medication error from adverse drug events in general.[33]

Non-adherence to medication and potentially inappropriate prescribing have been included in other reviews[32,33] but were excluded from this systematic review. Non-adherence, may represent an intentional decision made by an individual patient rather than the unintentional over or underuse of medication, that is, medication error. Inappropriate prescribing refers to the use of a drug where the risk of an adverse drug event outweighs the clinical benefit, particularly if a safer or more effective alternative therapy is available.[34] Potentially inappropriate prescribing refers to such inappropriate prescribing as identified by standardised tools such as Beer's criteria and STOPP/START.[35] Not all potentially inappropriate medications detected in this manner necessarily represent medication error however. The possibility exists of an intentional and informed decision on the part of the prescriber rather than the occurrence of true medication error.

### *Overall completeness and applicability of evidence:*

Because of the heterogeneity of the included studies, a meta-analysis could not be performed.

Half of the included studies examined the economic impact of medication error within a specific patient group and hence the results may not be generalizable to a general patient population.

Additionally, the majority of studies used a broad definition of medication error and did not stratify individual types of medication error in their cost analysis. Hence, the evidence was insufficient to identify the



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types of medication error most likely to result in economic burden or to identify a particular group of health care professionals responsible for errors likely to result in economic burden.

Errors of omission were absent from the included studies. Hence, where medication costs are used to calculate the economic impact of medication error, the true economic burden may be underestimated.

None of the studies looked at economic implications from a patient or societal perspective. Indirect costs were largely absent from studies to date with no studies considering costs such as loss of earnings. Quality of life was not considered in any of the included studies. This is in keeping with the findings of a recent review conducted by Patel *et al.* of approaches used for calculating the cost of medication errors.[36] In addition, the costs explored from a primary care perspective were limited, and costs pertaining to time of general practitioners and pharmacists were absent. GPs and community pharmacists as accurate providers of patients' medication information, play a key role in reducing medication error.[37] A study conducted in the UK found that a pharmacist involved in dispensing a prescription with errors or missing information spent on average 5.7 min. per problem with a range from 0.2–48 min.[38] A similar time burden amongst GPs is likely and would suggest a significant unexplored economic burden.

*Quality of the evidence:*

As methodology varied between studies and details of how cost information was obtained was lacking in a number of studies, it is not surprising that a lack of consistency was identified between results. An overall absence of high quality studies in this area was highlighted with only one study[18] fulfilling all applicable quality criteria. Additionally, reported costs in three studies were based on potential costs as decided by an expert panel.[19,25,29] The potential for subjectivity exists, and evidence from the opinion of expert groups has traditionally been regarded as the lowest level in the hierarchy of levels of evidence.[39]

*Potential biases in the review process:*

The year of publication was used in four of the included studies to inflate costs to 2015 values as no year was specified in the studies. This could result in a potential inaccuracy if the cost information was in fact obtained in an earlier year. The review was limited to English language publications and as grey literature was not sought may also be subject to a publication bias. Assessment of study quality was challenging because of variability in terms of study design of the included studies. The approach used for quality assessment was applicable to all of the included studies but only assessed quality from economic and error reporting perspectives. Standardised tools assessing quality from an epidemiological perspective could not be applied universally to the studies.[40] Additionally, other checklists for critical appraisal of economic studies pertained specifically to economic evaluations and could not be applied.[41,42]

*Recommendations:* In order to allow meaningful comparison between studies assessing the economic impact of medication error, standardisation in terminology pertaining to medication error is required. Future studies should provide additional information on firstly the types of medication error being costed and secondly, the consequences of errors in terms of patient harm. The recent EMA guidance on recording, coding, reporting and assessment of medication errors has the potential to enhance future work in this area.[12] Future studies would be strengthened by applying a case–control design so that incremental costs can be calculated. Greater detail is also required from an economic perspective. Clear descriptions of cost sources and explicit cost calculations are required as recommended by Patel *et al.* in their recent review of approaches for calculating the cost of medication errors.[36] Additionally, the timeframe during which the costs are calculated should be specified. A greater breadth of costs also needs to be explored in future studies. Direct costs, indirect costs and psychosocial costs should all be included to determine the true economic burden of medication error.

## CONCLUSION

This systematic review suggests that the true economic impact of medication errors has not been accurately estimated to date. Studies evaluating the economic impact of medication error have been primarily conducted among hospital inpatients and have focused mainly on the hospitalisation costs associated with medication error. Variability was detected in methodology and many studies were of poor quality. Future work is required firstly to assess the economic impact of individual types of medication error and secondly to assess economic impact in a broader context inclusive of primary care, patients and society.



DOI: 10.1002/pds

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

### KEY POINTS

- Medication error is a significant source of preventable patient morbidity and mortality. An accurate estimate of the economic burden of medication error is required to inform interventions focussing on its reduction.
- Considerable variability existed between studies in terms of types of medication error assessed and study quality. In terms of economic impact; the mean costs per medication error per study ranged from €2.58 to €111 727.08.
- Variability among the studies in the patients, settings, errors included and costing approach limits the interpretation of these figures.
- Direct costs as measured by healthcare costs were identified as the predominant measure of the economic impact of medication error.
- To date assessment of the economic impact of medication error has been predominantly hospital based with little information on economic impact from a primary care or a patient perspective.

## ETHICS STATEMENT

The systematic review included only published studies assessing the economic aspect of medication error. No person can be identified or have information associated with them in any of the studies included in the review. Therefore we do not consider this study to constitute human subjects research. This has not been confirmed by an institutional review board or ethics committee.

## ACKNOWLEDGMENTS

The authors gratefully acknowledge the help of Professor John Browne and the UCC Graduate Studies Office who provided the module entitled 'Systematic reviews for the Health Sciences' and the help of Mr Joe Murphy, librarian, Mercy University Hospital, Cork.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.



DOI: 10.1002/pds