A systematic review of approaches for calculating the cost of medication errors

Krishan Patel,¹ Robert Jay,¹ Muhammad Waseem Shahzad,² William Green,³ Rakesh Patel¹

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/ejpharm-2016-000915>).

¹Biological Sciences and Psychology Department of Medical & Social Care Education, College of Medicine, Leicester, UK
²School of Management, University of Leicester, University Road, Leicester, UK
³Operations and Knowledge Management—School of Management, University of Leicester, University Road, Leicester, UK

Correspondence to

Dr Krishan Patel, Biological Sciences and Psychology Department of Medical & Social Care Education, University Hospitals of Leicester NHS Trust—College of Medicine, 107 Princess Road East, Leicester LE1 7LA, UK; krishan.patel@nhs.net

Received 8 February 2016

Revised 5 May 2016

Accepted 10 May 2016

Published Online First

8 June 2016

ABSTRACT

Introduction Although medication errors may cause significant morbidity and mortality, the true cost of avoidable harm from such errors is unclear. While studies describe different methods for calculating a financial cost from an error, there remains variability in the way calculations are conducted depending on the clinical context. This review aimed to investigate the range of approaches for calculating medication error costs across healthcare settings.

Methods A systematic review was carried out with a duplicate data extraction approach and mixed methods data synthesis. Medline, Embase and Web of Science were searched for studies published between 1993 and 2015. Studies that explicitly described a method for calculating medication error cost were included. The variables used for the calculations and a description of the approach for calculating errors were reported.

Results 21 studies were included in the final review. There was wide variation in the way calculations were undertaken, with some calculations using a single variable only and others using several variables in a multistep approach. Few calculations included indirect costs, such as loss of earnings for the patient, and only one calculation considered opportunity cost. The majority of studies presented direct medication error costs whereas others approximated error costs from the savings made following an intervention.

Conclusions There are a wide range of methods used for calculating the cost of medication errors. The diversity arises from the number of variables used in calculations, the perspective from which the calculation is conducted from, and the degree of economic rigour applied by researchers.

INTRODUCTION

A significant component of avoidable harm in any healthcare system can be attributed to medication errors (MEs).¹ Although there are a number of interventions for reducing MEs such as pharmacy reconciliation or electronic prescribing systems, accurately estimating the degree of harm avoided or the overall benefit of the intervention to the healthcare system remains challenging. Many different approaches were used to calculate the cost of MEs. The differences varied in the degree of accuracy of the calculation and the degree of justification used by researchers when using one approach over another. Furthermore, there was no consistency or consensus for using one approach over another in the same clinical context. Thus, as well as the difficulty of accurately calculating the true cost of an ME, there is the additional challenge of making reliable cost comparisons for errors across care

contexts. Moreover, the term ‘medication error’^{2–4} does not yet have a formal consensus on its definition.

Difficulties around calculating the cost of an ME stem from the possibility of the event taking place at any time in the patient journey. An error can occur at any point from the initial presentation of a condition, across care contexts and between different professionals. This produces great variability in the outcome of MEs and subsequent difficulty in having an overarching approach to estimate the cost of their impact. An example to illustrate this difficulty could be costing errors from vaccinations versus chemotherapy, which are given in contrasting settings and have differing ways in which an error may manifest. Furthermore, an ME can alter the course of a clinical presentation, for example, the failure of dose adjustment and consequent inappropriate dosing of antibiotics in patients with kidney disease. Therefore, deciphering the true outcomes or consequences, independent of the natural history of a condition, is tough and can be subjective. Continuing the same example above, determining the additional number of nights in hospital solely as a result of their ME as opposed to the natural history of their underlying illness is subjective.

The struggle in calculating the cost of MEs over and above other healthcare interventions is largely due to the difference in consequences between one error and another as well as the differences in consequences across patients and clinical context. Traditional study designs such as experimental or quasi-experimental rely on matched patients; however, finding true matches for the consequences or side effects of MEs is difficult. This leads to sufficient subjectivity in the application of methods for calculating error across care contexts. Finally, some calculations use mainly direct costs, such as the increase in raw cost of a medication to treat a patient following an error,⁵ whereas others use specific indirect costs or equate the entire cost of the subsequent care incurred after an error^{6–8} in the calculation for evaluating cost. This implies that some methods may incorrectly estimate the cost of MEs but more importantly that setting the viewpoint from which the errors are calculated is essential.

This variation in methodologies has implications for how the consequent interventions, aimed at reducing MEs, are evaluated in cost-benefit and effectiveness analyses. Aside all the problems that result from inconsistency in the use of different methods, few approaches are underpinned by methodologies used in health economics.

CrossMark

To cite: Patel K, Jay R, Shahzad MW, et al. *Eur J Hosp Pharm* 2016;**23**:294–301.

Furthermore, there is also a lack of understanding around how to group different methodologies for calculating MEs in a given clinical context or for a given type of ME. The aim of this review is to identify the approaches used for calculating the cost of an ME across healthcare settings to facilitate future research and evaluation of interventions.

METHODS

Definitions

This review specifically looks at MEs, which are different to prescribing errors and adverse drug events (ADEs). ME incorporates prescribing error⁹ within its definition but is not as broad as the definition for ADE,¹⁰ which also includes adverse drug reactions. The definition of MEs used in this review is taken from the European Medicines Agency as 'A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient'.³

Search strategy

This review satisfies the conditions for systematic reviews described by Grant and Booth.¹¹ The authors took guidance from the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and Centre for Reviews and Dissemination guidelines (which have a specific focus on reviews for adverse events) to ensure the methodology met accepted criteria required of systematic reviews.^{12 13} An environmental scan of the literature gave a broad overview of the methodologies surrounding the cost of an ME. A review of relevant studies set the context of the review and generated criteria against which subsequent studies were compared.

This review sourced studies from Medline, Embase and Web of Science. There was no review protocol that could be identified for this particular subject area. The searches were carried out on 14 August 2015 and contained publications from all study types dating back to January 1993. In 1993, the problem of MEs was brought to the fore by Bates *et al*,¹⁴ who also was one of the first researchers to investigate the cost of this problem in healthcare. The search string contained a number of key words and associated synonyms linking 'medication' and 'error'

to 'economics' and 'cost'. See online supplementary appendix 1 for details of the search used in Medline and Embase. Scope notes for each search concept were reviewed. Duplicate studies were screened for within the search string. Two authors reviewed all of the titles and abstracts and subsequently applied the inclusion and exclusion criteria. The titles and abstracts were read to exclude publications, which did not mention MEs and their potential economic impact. Publications were also excluded if they were not in the English language or if they did not originate from peer-reviewed literature, for example conference proceedings. No exclusions based on originating journal or study type were applied given the relatively few number of studies investigating methods for calculating ME cost. After sourcing the articles, the full texts were analysed specifically for any methodologies for calculating the cost associated with an ME. Those studies that did not specifically allude to how a cost was attributed to an ME were excluded (see figure 1). This was the first systematic review for calculating the cost of MEs and no criteria for reviewing bias across these methods were identified from the environmental scan. As a consequence, any source of bias resulting from the application of calculations by researchers was investigated during this review. Any attempts made by researchers to mitigate against bias were noted during the data extraction phase.

Data synthesis

Two authors (KP and RJ) developed a data extraction table, which was initially piloted and then released to all the authors. The table was refined through an iterative process of feedback to improve the ease and consistency of extracting data from the studies. All authors were involved in data extraction and each paper had data extracted by two authors. Any disparity over the interpretation and categorisation of the data was discussed with at least one additional author present and an agreement was reached by consensus. Inter-rater agreement was not formally measured. Table 1 presents a taxonomy for the range of inputs used to calculate ME costs that was generated from the discussion between all authors about the 21 abstracts used within the review. This table ensured there was little variability in the interpretation made by authors when extracting data

Figure 1 Flow chart of study selection.

Table 1 Terminology used to describe inputs of calculations

Classification of costs included in calculations	Glossary of terminology
Pharmaceutical	To include the terms below
Medication cost	Raw pharmaceutical cost of the drug involved in the error
Drug monitoring	Any procedures/investigations required to maintain a drug within its therapeutic range
Investigations	Any tests undertaken with therapeutic intent
Laboratory	To include all pathology services
Radiology	To include all imaging modalities
Procedures	Any examination or intervention with a therapeutic intent
Diagnostic	Examination or interventions to determine a condition or disease
Invasive monitoring	Interventions that involve break of the skin to observe body functions
Surgical	Interventions that involve break of the skin with therapeutic intent
Therapies	Synonym of procedure
Labour	The sum of all wages paid to employees
Pharmacist	Wages paid to pharmacists
Physician	Wages paid to doctors/physicians
Services	Cost of providing a particular facility for a patient's care
Outpatient care	Cost of hospital-based clinics and associated investigations and treatments
Home visits	Cost of patient care in their own home
Transport/ambulance	Cost of patient transport
Ambulatory care	Cost of a hospital visit short of an admission
Rehabilitation stay	Cost of a stay at a rehabilitation centre
Nursing facility stay	Cost of a stay at a nursing facility
Emergency department visit	Cost of a visit to the emergency department
Intensive care stay	Cost of admission to an intensive care unit
Infrastructure	Cost of physical facilities for delivering healthcare
Bed	Cost of providing physical facilities and care surrounding an individual patient's treatment
Overheads	Operating expenses not directly related to a single patient admission—typically a fixed cost
Equipment	Cost of consumables used to deliver patient care
Medical supplies	Cost of consumables used to deliver patient care
Hospital admission	Sum of all variable costs that can be attributed to a single patient
Patient	Any cost borne by the consumer of the service
Cost of permanent harm	Estimation of the cost of living with any lasting consequence of a medication error
Income	Loss of patient income due to increased time spent in hospital as a result of a medication error
Economic	Accounting cost plus opportunity cost
Opportunity costs	The cost of an alternative that must be forgone in order to pursue a certain action

from the studies. The publications were examined to identify factors such as setting, study design and length of study for the purposes of bringing greater context and clarity to the findings. The mode of prescription and the type of medications analysed were identified to find any association with the chosen methodology of calculating the cost of MEs. It is beyond the scope of this review to analyse the severity of MEs or their aetiology; therefore, it was simply reported whether or not there was any

evidence of consideration for these factors within the study designs.

The definition of MEs covers a number of potential stages in the process from prescription to administration for an error to occur. Each study was analysed to see which stages in the Medicines Use Pathway¹⁵ were investigated to detect MEs. This consists of four distinct stages: (1) prescribing medication, (2) supply/dispensing of medication, (3) administration of medication and (4) review of the effects of medication.

From the environmental scan, it was evident that some studies examined the impact of MEs within the context of an intervention aimed at reducing the number or impact of those errors. Therefore, the nature of those interventions, where applicable, was also noted.

Finally, and most importantly, the calculation of costs of MEs was identified. Particular focus was given to the type of costs that were included in the calculation and whether the cost incurred was directly related to the patient's treatment or otherwise. Direct costs were defined as any costs incurred by the healthcare provider in order to deliver their services to patients. Indirect costs were defined as costs incurred by other parties not directly involved in the delivery of healthcare. Economic costs would include accounting cost plus opportunity cost, which is defined as the cost of an alternative that must be forgone in order to pursue a certain action.

RESULTS

The literature search heralded 1133 potentially relevant studies. Duplicate studies were filtered within the search command. After applying the exclusion criteria to the publication abstracts, the 48 potentially relevant abstracts were singled out. Reading the full articles and excluding those without explicit evidence of calculating cost of an ME finally left 21 publications for the analysis (see figure 1).

Description of studies

As illustrated in table 2, 10 studies originated from USA, two from France, two from Germany and one each from Iraq, Iran, Israel, Mexico, Holland, Canada and Switzerland. With respect to clinical areas, 16 studies focused on secondary care (defined here as any inpatient hospital setting), two on both primary and secondary care and three studies on primary care alone.

Within secondary care, 15 publications focused on inpatient prescriptions and one on ambulatory care prescriptions. The majority (n=14) of studies did not specify particular groups of medications in their analysis and were therefore assumed to include all prescribed medications. There was a wide variation in the approach to grading MEs. Some studies did not allude to any form of grading system for type or severity, while other studies discussed preventability^{10 17 22 24} or attributed a level of harm that ensued.^{7–10 28 29} Only two studies used a previously validated methodology of measuring severity of an ME.^{23 26} With regard to the aetiology of MEs, 11 studies showed at least some evidence of acknowledging or considering the factors contributing to or causing errors.

Medicines use pathway

Categorising studies by the medicines use pathway showed that most studies (n=17) focused on MEs in the prescribing phase, where the decision is made as to whether a medicine is needed. Fewer studies showed evidence of considering errors occurring at supply/dispensing (n=4), administration (n=8) and in the monitoring of the response to medicines (n=7). Noted was a

Table 2 Studies calculating the cost of medication errors (MEs)

Study	Country	Clinical area	Prescribing mode	Study design	Length of patient follow-up	Intervention	Medication	Grading of MEs	Aetiology considered	Medicines use pathway stage	Inputs of calculation for MEs (indirect/opportunity costs in bold)
1. Aceves-Avila <i>et al</i> (2011) ⁶	Mexico	Primary care (outpatients)	Paper	Prospective cohort	6 months	No	Any	No	Yes	3 and 4	Medication cost+ patient's income foregone
2. Al-Ilela <i>et al</i> (2012) ¹⁶	Iraq	Primary care	Unclear	Time-motion and cost analysis	Minimum of 2 days/50 doses	No	Vaccines	No	No	3	Medication cost+cost of labour (microcosting methodology)
3. Bates <i>et al</i> (1997) ¹⁷	USA	Secondary care	Paper	Nested case control, prospective cohort	6 months	No	Any	Yes	No	Unclear	Not specified (overall costs from treatment at a particular unit)
4. Cullen <i>et al</i> (1997) ¹⁰	USA	Secondary care	Unclear	Prospective cohort	6 months	No	Any	Yes	Yes	1, 2, 3 and 4	(Overall length of stay)+pharmacy cost+laboratory costs+surgical costs
5. Dennehy <i>et al</i> (1996) ⁷	USA	Secondary care	Unclear	Retrospective review	1 month	No	Any	Yes	Yes	1, 3 and 4	Not specified (all direct and indirect costs for a hospital visit associated with a medication error)
6. Field <i>et al</i> (2005) ⁸	USA	Secondary care (ambulatory care)	Unclear	Retrospective cohort	12 months	No	Any	Yes	Yes	1	Cost of hospital stay+nursing facility stay+rehabilitation stay+ED visit+ambulatory care+physician wage+diagnostic tests+therapies+laboratory tests+ambulances+medical equipment+home visits+medication
7. Gharekhani <i>et al</i> (2014) ¹⁸	Iran	Secondary care	Unclear	Prospective cross-sectional	18 months	Yes	Any	No	Yes	1 and 3	Medication cost
8. Glowacki <i>et al</i> (2003) ¹⁹	USA	Secondary care	Paper	Prospective cohort	23 non-consecutive days in 3 months	Yes	Antibiotics	No	Yes	1 and 3	Medication costs preintervention and postintervention (+pharmacist wage to identify the MEs)
9. Hellinger and Encinosa (2010) ²⁰	USA	Primary and secondary care	Unclear	Retrospective review and cohort comparison	12 months	No	Antiretrovirals	No	No	1	Medication cost
10. Hohl <i>et al</i> (2011) ²¹	Canada	Secondary care	Unclear	Prospective observational	3 weeks	No	Any	No	No	1 and 4	Costs of hospital admission+outpatient care+ED visit+surgical procedures
11. Hoonhout <i>et al</i> (2010) ²²	Holland	Secondary care	Unclear	Three-stage retrospective review	Not specified	No	Any	Yes	Yes	1, 2, 3 and 4	Cost of staff+drugs+equipment+overheads+beds+additional procedures
12. Lampert and Kraehenbuehl (2008) ²³	Switzerland	Secondary care	Unclear	Prospective observational	32 weeks	Yes	Any	Yes	Yes	1	Medication cost
13. Meier <i>et al</i> (2015) ²⁴	Germany	Primary care	Unclear	Prospective cohort	3× 1 months	No	Any	Yes	Yes	1	Not specified (cost of entire stay for ME-related admission)
14. Meissner <i>et al</i> (2009) ²⁵	USA	Secondary care	Unclear	Cost accounting	2× 12 months	No	Opioid patient controlled analgesia	No	Yes	1, 2, 3 and 4	Medication cost+laboratory tests+radiology+hospital stay+medical supplies+labour+ opportunity costs
15. Nerich <i>et al</i> (2013) ⁹	France	Secondary care	Electronic	Prospective observational	11 months	Yes	Antineoplastic	Yes	No	1	Medication cost+pharmacist wage+cost of hospital stay
16. Ojeniran <i>et al</i> (2010) ⁵	Israel	Secondary care	Unclear	Retrospective cross-sectional	6 weeks	No	Antibiotics	Yes	No	1	Medication cost
17. Ranchon <i>et al</i> (2011) ²⁶	France	Secondary care	Paper	Prospective cohort	12 months	No	Antineoplastic/chemotherapy	Yes	Yes	1, 2 and 4	Not specified (overall cost of treating the complication)

Continued

Table 2 Continued

Study	Country	Clinical area	Prescribing mode	Study design	Length of patient follow-up	Intervention	Medication	Grading of MEs	Aetiology considered	Medicines use pathway stage	Inputs of calculation for MEs (indirect/opportunity costs in bold)
18. Rottenkolber <i>et al</i> (2012) ²⁷	Germany	Secondary care	Unclear	Retrospective cross-sectional review	12 months	No	Any	No	No	Unclear	Costs of personnel+non-personnel +infrastructure (every resource consumed—microcosting methodology)
19. Samp <i>et al</i> (2014) ²⁸	USA	Primary and secondary care	Unclear	Prospective cross-sectional	2 weeks	Yes	Any	Yes	No	1	Medication cost+pharmacist+drug monitoring+estimated cost of permanent harm to patient
20. Schneider <i>et al</i> (1995) ²⁹	USA	Secondary care	Unclear	Retrospective cohort	24 months	No	Any	Yes	No	1	Costs of laboratory+non-invasive procedures +invasive monitoring/procedures+length of stay+intensive care
21. Waddell <i>et al</i> (1998) ³⁰	USA	Secondary care	Unclear	Prospective cohort	8 months	Yes	Any	No	No	1	Medication cost

variation in the terminology used to describe MEs, with some studies reporting on ADEs and other similar phrases.

Calculation of medication errors

As illustrated in table 3, of the 21 identified studies that specifically outlined a strategy for calculating the cost of MEs, six used an intervention aimed at reducing MEs and then equated the resultant cost savings to the cost of MEs. The remaining 15 studies observed MEs and calculated the cost of the events occurring as a consequence.

There was a wide variety in the inputs used to estimate the cost as a result of an ME (table 2—inputs of calculation for ME). The review revealed eight types of inputs used for calculating the cost of MEs (table 1). The inputs used by studies in their calculations were classified and represented in table 4.

Direct costs

Some studies used the raw pharmaceutical cost of a medication to estimate the cost of an error^{5 6 18–20 23 30} and this was the only single direct cost involved in the calculation. Others expanded on this basic methodology, adding in additional direct costs related to the cost of a hospital stay, laboratory tests and labour costs.

Indirect and opportunity costs

Few studies assessed beyond direct costs; three studies mention indirect costs with Aceves-Avila *et al*⁶ including the cost of a patient's wage for a day lost in their calculation and Samp *et al*²⁸ including the cost of permanent harm to the patient in their costing. Meissner *et al*²⁵ was the only study to consider the true economic cost of MEs by including opportunity cost in addition to just the accounting costs reported by all of the other studies.

Bias

Only four studies^{14 17 21 27} used internal controls as part of the study design. Two studies^{9 28} included a sensitivity analysis within the calculation for costing MEs. There was little evidence of any formal consideration of bias by other researchers across the remaining studies.

DISCUSSION

This systematic review was conducted to investigate approaches for calculating the cost of MEs since there is a need to accurately quantify the impact of interventions for reducing avoidable

Table 3 Classification and types of calculation

Method of calculation	No of studies (%)
Studies directly calculating the cost of a medication error	15 (71)
Studies deriving the cost of a medication error through an intervention	6 (29)
Number of direct costs taken into account in the calculation	
1	7 (33)
2	1 (5)
3+	9 (43)
Not specified	4 (19)
Calculations taking into account only direct costs	17 (81)
Calculations taking into account indirect costs (see table 2)	3 (14)
Calculations taking into account opportunity costs (see table 2)	1 (5)

Table 4 Types of cost considered by each study

Classification of costs	Study number																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Pharmaceutical																					
Medication cost	✓	✓				✓	✓	✓	✓		✓	✓		✓	✓	✓			✓		✓
Drug monitoring																			✓		
Investigations																					
Laboratory				✓		✓								✓						✓	
Radiology														✓							
Procedures										✓	✓									✓	
Diagnostic						✓															
Invasive monitoring																					
Surgical				✓																	
Therapies						✓															
Labour		✓									✓			✓				✓			
Pharmacist				✓				✓							✓				✓		
Physician						✓															
Services										✓											
Outpatient care						✓															
Home visits						✓															
Transport/ambulance						✓															
Ambulatory care						✓															
Rehabilitation stay						✓															
Nursing facility stay						✓															
Emergency department visit										✓											
Intensive care stay																				✓	
Infrastructure																		✓			
Bed											✓										
Overheads											✓										
Equipment											✓										
Medical supplies						✓								✓							
Hospital admission			✓		✓	✓				✓			✓	✓	✓		✓			✓	
Patient																					
Cost of permanent harm																			✓		
Income	✓																				
Economic																					
Opportunity costs														✓							

harm. The findings demonstrate that a standardised approach for exploring the costs of MEs was lacking; therefore, the development of valid and reliable methods for undertaking calculations is necessary before the impact of interventions for reducing MEs can be known.

This systematic review showed a general inconsistency in the terminology and methods used by researchers for calculating ME costs, which may be as a result of the lack in an accepted methodology or guidance as to how to approach calculations. The systematic review yielded a relatively low number of studies and this may be due to the interest in this area being scant until relatively recently. Furthermore, no studies identified in the review were conducted within an National Health Service (NHS) setting, confirming that the calculation of true costs following MEs remains unknown in the UK. The cost inputs within the calculations were also not explicitly defined and varied across studies, so understanding how calculations can be applied across clinical contexts is unclear. Meissner *et al*²⁵ and Hoonhout *et al*²² described using labour costs in their calculations. Both studies were conducted in different countries and

therefore the meaning of labour costs, in the absence of further clarification, was unknown. Similarly, Al-Iela *et al*¹⁶ and Rottenkolber *et al*²⁷ used a microcosting method but applied the approach differently in both studies. Al-Iela *et al*¹⁶ added only medication costs to labour costs to derive a cumulative cost, whereas Rottenkolber *et al*²⁷ also included infrastructure, pharmaceutical and personnel costs as part of the calculation.

There was wide variation in the way similar calculations were conducted across studies since the number of inputs and stages within a given calculation was inconsistent. Lampert *et al*²³ used a single input cost for a single stage calculation to investigate the cost of MEs, whereas Rottenkolber *et al*²⁷ used multiple inputs ('every resource consumed') into a multistage calculation for costing MEs. Aceves-Avila *et al*⁶ calculated MEs using two inputs, for example, cost of medication and cost of a day's income for the patient, whereas Field *et al*⁸ generated multiple inputs by taking into account the wider costs within the clinical environment. Field *et al*⁸ inputted many costs including inpatient, outpatient and personnel costs and compared the difference 6 weeks before and after an ME. The diversity among

the various cost inputs used demonstrates the inherent difficulty for researchers in deciding upon and costing all the relevant costs into a given calculation.

The findings from this review also confirmed that the assignment of costs incurred following an ME was heavily based on the subjective judgement of the researchers. There was no consensus or an accepted standard method for calculating the cost of MEs. In the absence of a standard approach and with many types of factors used for calculating ME costs, the findings from the studies are open to bias. Schneider *et al*²⁹ inputted costs for inpatient stay, procedures, laboratory tests and intensive care into their calculation; however, evidence or justification for how, if at all, all these outcomes were relevant or actual consequences from the ME(s) was lacking. Dennehy *et al*⁷ used the entire cost of the hospital stay in the calculation to mitigate against any subjective decision-making. Conversely, Bates *et al*¹⁷ used a cohort of control patients who suffered no harm to compare costs with those patients who suffered from an ME. Nerich *et al*⁹ justified the choices of inputs into their calculation by asking experts to judge the likelihood of clinical sequelae being attributable to a particular ME. These various approaches demonstrate the difficulty and complexity in determining causality between a specific ME and subsequent events following it.

A number of studies^{9 18 19 23 28 30} attempted to calculate the cost of an ME indirectly by estimating the cost reduction from preventing errors following an intervention. The cost of the MEs calculated in this way varied depending on the nature and effectiveness of the intervention in a particular care context. Oftentimes, costs of the intervention were mixed into the calculations. Glowacki *et al*¹⁹ used a pharmacist-led intervention for reducing ME. In this calculation, the cost of the pharmacist's time was included when estimating the cost reduction from reducing MEs following the intervention. The validity for using such approaches is questionable. Including costs of an intervention into a calculation and measuring the resultant cost savings may underestimate the true cost of an ME. Furthermore, other costs that were not influenced by the chosen intervention may be missed from the calculation, but this is beyond the scope of this study.

Although many studies used methods for calculating ME derived from perspective of the healthcare provider, some studies took into account costs from the perspective of others. Aceves-Avila *et al*⁶ included a simple indirect cost into their calculation in the form of a single day's wage forgone for the patient as a result of an error. Samp *et al*²⁸ focused more heavily on indirect cost by including into the calculation the cost of any permanent harm to the patient as a result of an ME. Meissner *et al*²⁵ took insight from health economics by combining the opportunity cost, or cost of missing out on an alternative, with the accounting cost of an ME. Samp *et al*²⁸ also takes an economic approach by using a decision tree analysis to model their data and probabilities of events occurring to structure potential scenarios for the calculation.

Finally, the findings from this review demonstrate that bias is a significant factor in the approaches used for calculating ME cost. Where researchers have used an intervention to generate an ME cost, there is also likely to be an inherent bias within their calculation.

CONCLUSION

This review confirms the wide variation in approaches to calculating the cost of MEs. The number of inputs or stages used by researchers in the calculations was largely responsible for the variation seen during the review. The findings highlight that,

while different methods may be appropriate in particular contexts, clear definitions and explicit cost calculations should be reported by researchers. A viewpoint or perspective should be presented early and used to justify the inclusion of direct and indirect costs. For example, the cost of an ME incurred by a patient may be different to that of a service provider or government; hence, different inputs or stages may be relevant in either context. There was notable variation in economic rigour applied to calculations; therefore, expertise from health economists could improve the accuracy of methods for costing MEs.

This systematic review had particular strengths in its broad search criteria and subsequent stringent exclusion criteria. The selected studies were therefore of sufficient detail to avoid making assumptions about the nature of methodologies for calculating MEs. The review was conducted in a systematic approach and there were multiple reviewers involved in extracting the data. A significant weakness would be the number of databases included in the search. Furthermore, a limitation of the review could be the small sample size of 21 studies, reducing the generalisability of the findings. No search updates were carried out following August 2015; therefore, studies beyond this date were not included. The lack of a widely accepted definition for MEs and the varying terminology used to describe this phenomenon may limit the completeness of this systematic review at this point in time. Finally, there is a lack of a standardised tool for measuring the quality of the individual studies.

The implications of this study will affect how people undertake economic evaluations of interventions aimed at reducing MEs. Further research is required to determine the most appropriate context-specific method for calculating ME costs, since MEs occur across all healthcare contexts and have costs that affect patients, institutions and wider economy or society. Given that there is no standardised or optimum method for calculating the cost of an ME, the findings from this review confirm good practice should include a justification of the approach used for calculating cost of ME in a given clinical context, including the relevant inputted costs.

Acknowledgements All the authors would like to thank the University Hospital of Leicester NHS Trust Clinical Librarian Service at the Leicester Royal Infirmary for the tremendous support provided throughout this study.

Contributors RP, KP and RJ conceived the idea for conducting the review. KP and RJ conducted the database searches. All authors (RP, KP, RJ, WG and MWS) extracted the data from the papers. The final manuscript was written and checked by all authors (RP, KP, RJ, WG and MWS).

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Pirmohamed M, James S, Meakin S, *et al*. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004;329:15–19.
- 2 Aronson JK. Medication errors: definitions and classification. *Br J Clin Pharmacol* 2009;67:599–604.
- 3 European Medicines Agency. Medication errors. 2015. http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000570.jsp. (accessed 25 May 2016).
- 4 U.S. Food and Drug Administration. Medication Errors. 2015 <http://www.fda.gov/drugs/drugsafety/medicationerrors/>. (accessed 25 May 2016).
- 5 Ojeniran M, Shouval R, Miskin IN, *et al*. Costs of appropriate and inappropriate use of antibiotics in the emergency department. *Isr Med Assoc J* 2010;12:742–6.
- 6 Aceves-Avila FJ, Benites-Godínez V, Ramos-Remus C. Cost of medication errors in rheumatic patients in Mexico. *Clin Rheumatol* 2011;30:1421–4.
- 7 Dennehy CE, Kishi DT, Louie C. Drug-related illness in emergency department patients. *Am J Health Syst Pharm* 1996;53:1422–6.
- 8 Field TS, Gilman BH, Subramanian S, *et al*. The costs associated with adverse drug events among older adults in the ambulatory setting. *Med Care* 2005;43:1171–6.

- 9 Nerich V, Borg C, Villanueva C, *et al.* Economic impact of prescribing error prevention with computerized physician order entry of injectable antineoplastic drugs. *J Oncol Pharm Pract* 2013;19:8–17.
- 10 Cullen DJ, Sweitzer BJ, Bates DW, *et al.* Preventable adverse drug events in hospitalized patients: a comparative study of intensive care and general care units. *Crit Care Med* 1997;25:1289–97.
- 11 Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Info Libr J* 2009;26:91–108.
- 12 Akers J, Aguiar-Ibáñez R, Baba-Akbari Sari A. *CRD's Guidance for Undertaking Reviews in Health Care*. York: Centre for Reviews and Dissemination (CRD), 2009.
- 13 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9.
- 14 Bates DW, Leape LL, Petrycki S. Incidence and preventability of adverse drug events in hospitalized adults. *J Gen Intern Med* 1993;8:289–94.
- 15 Wright J, East and South East England Specialist Pharmacy Services. Optimising medicines use in care pathways using pharmacy support. 2014. http://www.medicinesresources.nhs.uk/en/Download/?file=MDs3OTIzMzk7L3VwbG9hZC9kb2N1bWVudHMvQ29tbXVuaXRpZXMuU1BTX0VfU0VFRW5nbGFuZC9PcHRpbWlzaW5nX21lZGljaW5lc191c2VfaW5fY2FyZV9wYXRod2F5cy5wZGY_.pdf. (accessed 25 May 2016).
- 16 Al-hela OQB, Bahari MB, Al-abbassi MG, *et al.* Estimation of immunization providers' activities cost, medication cost, and immunization dose errors cost in Iraq. *Vaccine* 2012;30:3862–6.
- 17 Bates DW, Spell N, Cullen DJ, *et al.* The costs of adverse drug events in hospitalized patients. *JAMA* 1997;277:307–11.
- 18 Gharekhani A, Kanani N, Khalili H, *et al.* Frequency, types, and direct related costs of medication errors in an academic nephrology ward in Iran. *Ren Fail* 2014;36:1268–72.
- 19 Glowacki RC, Schwartz DN, Itokazu GS, *et al.* Antibiotic combinations with redundant antimicrobial spectra: clinical epidemiology and pilot intervention of computer-assisted surveillance. *Clin Infect Dis* 2003;37:59–64.
- 20 Hellinger FJ, Encinosa WE. The cost and incidence of prescribing errors among privately insured HIV patients. *Pharmacoeconomics* 2010; 28:23–34.
- 21 Hohl CM, Nosyk B, Kuramoto L, *et al.* Outcomes of emergency department patients presenting with adverse drug events. *Ann Emerg Med* 2011;58: 270–279.e4.
- 22 Hoonhout LHF, de Bruijne MC, Wagner C, *et al.* Nature, occurrence and consequences of medication-related adverse events during hospitalization. *Drug Safety* 2010;33:853.
- 23 Lampert ML, Kraehenbuehl S, Hug BL. Drug-related problems: evaluation of a classification system in the daily practice of a Swiss University Hospital. *Pharm World Sci* 2008;30:768–76.
- 24 Meier F, Maas R, Sonst A, *et al.* Adverse drug events in patients admitted to an emergency department: an analysis of direct costs. *Pharmacoepidemiol Drug Saf* 2015;24:176–86.
- 25 Meissner B, Nelson W, Hicks R, *et al.* The rate and costs attributable to intravenous patient-controlled analgesia errors. *Hosp Pharm* 2009;44:312–24.
- 26 Ranchon F, Salles G, Spath HM, *et al.* Chemotherapeutic errors in hospitalised cancer patients: attributable damage and extra costs. *BMC Cancer* 2011; 11:478.
- 27 Rottenkolber D, Hasford J, Stausberg J. Costs of adverse drug events in German hospitals—a microcosting study. *Value Health* 2012;15:868–75.
- 28 Samp JC, Touchette DR, Marinac JS, *et al.* Economic evaluation of the impact of medication errors reported by US clinical pharmacists. *Pharmacotherapy* 2014;34:350–7.
- 29 Schneider PJ, Gift MG, Lee YP, *et al.* Cost of medication-related problems at a university hospital. *Am J Health Syst Pharm* 1995;52:2415–18.
- 30 Waddell JA, Solimando DA Jr, Strickland WR, *et al.* Pharmacy staff interventions in a medical center hematology-oncology service. *J Am Pharm Assoc (Wash)* 1998;38:451–6.