YHEC
York Health Economics Consortium

The Newcastle upon Tyne Hospitals NHS
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Appendix F.2:

NICE Medicines Optimisation guideline: Cost-effectiveness of medicine reconciliation to reduce sub-optimal use of medicines and medicine-related patient safety incidents

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Draft Report

MICHELLE JENKS, Research Consultant
JAMES MAHON, Associate
MICK ARBER, Information Specialist

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Correspondence to: Michelle Jenks
York Health Economics Consortium (YHEC)
Level 2 Market Square
University of York
YORK
YO10 5NH
Tel: +44 (0)1904 323620

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Section 1: Introduction

1.1 BACKGROUND

Medicine reconciliation is the process of "identifying the most accurate list of a patient's current medicines – including the name, dosage, frequency and route – and comparing them to the current list in use, recognising any discrepancies, and documenting any changes, thus resulting in a complete list of medications, accurately communicated" (Institute for Healthcare Improvement, 2014). Analysis around the cost-effectiveness of medicines reconciliation was identified as being high priority by the Guidance Development Group (GDG). Wide variation in practice in the frequency and methods of medicine reconciliation exists, and as such the GDG agreed that it was important to assess the clinical and cost-effectiveness of this intervention to aid their making of recommendations. The economic modelling aimed to answer the following question:

- What is the effectiveness and cost-effectiveness of medicines reconciliation to reduce sub-optimal use of medicines and medicines-related patient safety incidents, compared to usual care?

A systematic review of cost-effectiveness evidence (reported in section 7 of the full guideline) identified one relevant study by Karnon *et al*. (2009). This economic evaluation was commissioned by NICE as part of the Patient Safety Pilot. The cost-utility analysis by Karnon *et al.* compared methods of medicine reconciliation at hospital admission, finding medicine reconciliation by pharmacists or pharmacist technicians to be dominant over usual care. This study was populated by data from observational studies which did not meet the inclusion criteria for the clinical evidence review on this topic. As such, the GDG requested for the decision-analytic model by Karnon *et al.* to be update utilising clinical evidence identified in the systematic review of clinical evidence (section 7) and other more recent data.

The use of decision-analytic models allows the cost and consequences of various interventions to be directly compared in order to assess which are the most effective and cost-effective.

In order to assess the cost-effectiveness of a particular intervention a standard unit of benefit is required, in order to compare across treatment areas. For example, if we cure a certain number of cases in one disease area and avert a certain number of events in another we need a common unit in order to decide which of these outcomes is more desirable. Health economics uses the quality-adjusted life year (QALY) for this purpose. The QALY incorporates the life years gained from a treatment strategy, adjusted for the quality of life that the person experiences during those years. Quality of life is determined using measures of utility which describe health-related quality of life, such as mobility, pain, ability to carry out usual functions, depression, on a scale of 0 to 1, with 1 being full health and 0

being dead. For example, if a person lives for 10 years with a utility of 0.5 they will gain 5 QALYs. If they live for 4 years with a utility of 0.75 they will gain 3 QALYs.

Cost-effectiveness analysis is based on the comparison of one intervention with another, such as standard care or no intervention. In order to do this it is the *incremental* QALYs and *incremental* costs that are considered. Most new interventions are more costly and also provide more health benefits. In order to decide whether the extra health benefits are worth the extra costs of the intervention, the incremental cost-effectiveness ratio is calculated. The ICER subtracts the cost of the current strategy from the cost of the new strategy, divided by the benefits of the current strategy subtracted from the benefits of the new strategy in order to determine the incremental cost per unit of benefit. The formula for calculating the ICER is shown below:

$$ICER = \frac{Cost_{New\ strategy} - Cost_{Old\ strategy}}{Benefit_{New\ strategy} - Benefit_{Old\ strategy}}$$

The higher the ICER, the higher the cost per QALY gained. NICE currently uses an ICER threshold of £20,000 to £30,000, above which an intervention is not deemed to be an efficient use of NHS resources. Where a new intervention is cheaper and more effective than its comparator it is known as being 'dominant' and where a new intervention is more expensive and less effective is it 'dominated'.

The cost-effectiveness decision rule can be rearranged to derive net benefit. During one-way deterministic sensitivity analysis it is often useful to calculate net benefit, rather than ICERs, to overcome difficulties in interpreting results including negative ICERs. The net benefit of an intervention can be calculated using the following formula:

$$\textit{Net benefit} = \textit{Threshold value} \times (Benefit_{New\ strategy} - Benefit_{Old\ strategy}) - (Cost_{New\ strategy} - Cost_{Old\ strategy})$$

Where the net benefit of a new intervention is positive the ICER will be below the opportunity cost threshold, whereas where the net benefit of a new intervention is negative the ICER is above the opportunity cost threshold.

1.2 STRUCTURE OF REPORT

The methodology used to conduct the analysis is described in Section 2. This includes an overview of the model structure, description of model input parameters and of the sensitivity analyses conducted. In Section 3 both the results of the base case analysis and sensitivity analyses are provided and in Section 4 these results are discussed, with limitations of the analysis highlighted.

Section 2: Methods

2.1 MODEL OVERVIEW

An economic model was constructed in *Microsoft Excel* to conduct a cost-utility analysis of medicine reconciliation compared to usual care (no medicine reconciliation). The structure of the model is show in Figure 2.1 and copies the structure of the model by Karnon *et al.* The decision-analytic model, models errors in medication following a prescription order. Each prescription order may result in either a medication error, or no error. Three types of medication errors are included within the model:

- An error of omission – a required drug is not supplied;
- An error of commission – the wrong drug, or dose is supplied;
- An error due to a known allergy – a drug is prescribed when it is known that the patient has an allergy to that drug.

For each error type there is a probability that the error will be detected prior to it reaching the patients. Where errors are not detected they may cause, or not cause harm. For errors causing harm, this harm is split into minor (caused by significant preventable adverse drug event (pADE), moderate (caused by serious pADE) or severe harm (caused by severe pADE)). The severity of each type of pADE is described by Karnon *et al.* (2009) as follows:

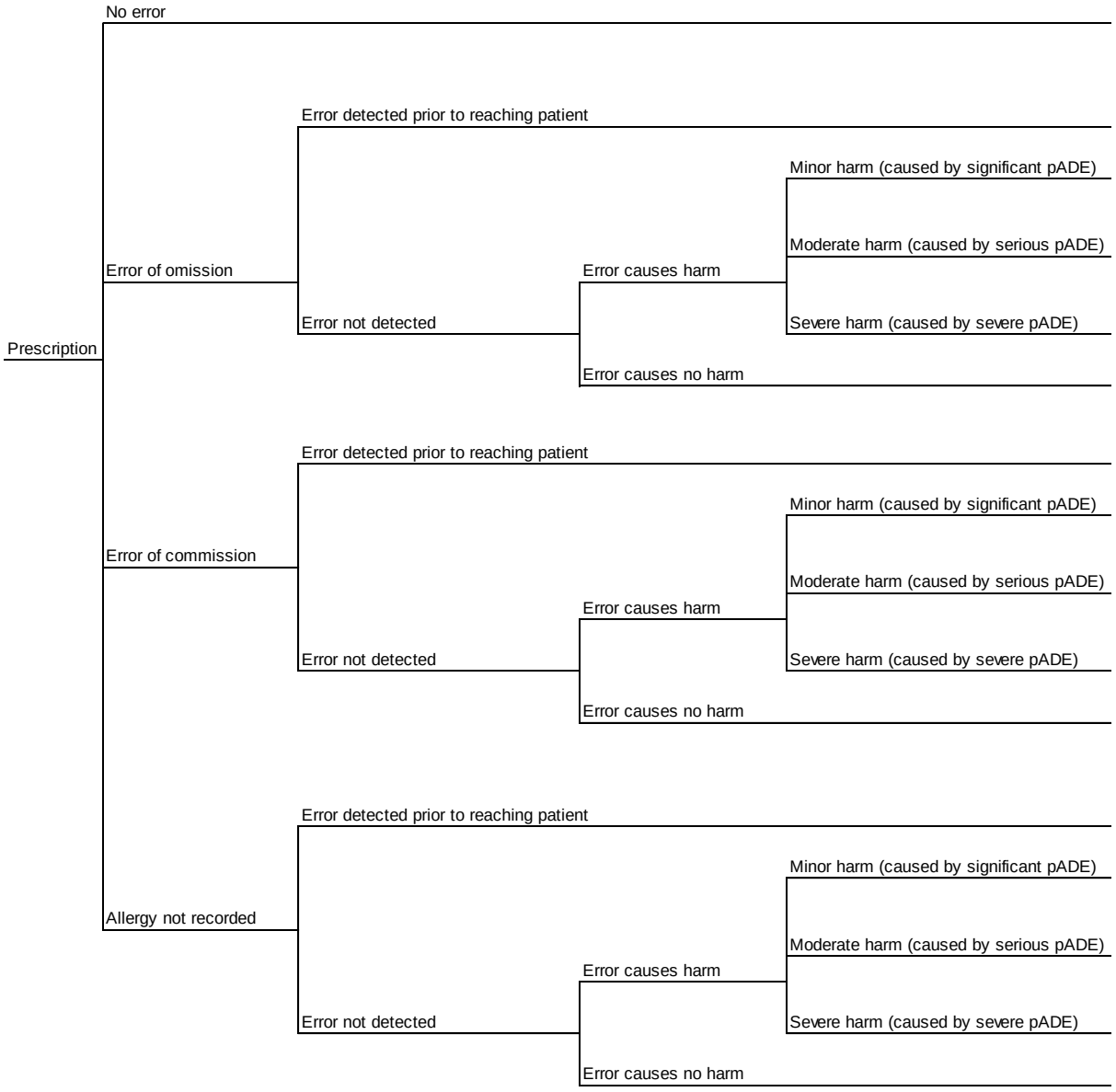
- Significant pADE results in temporary harm to the patient and requires intervention;
- Serious pADE results in temporary harm to the patients and requires initial or prolonged hospitalisation;
- Severe, life threatening or fatal pADE results in permanent patient harm, requires intervention to sustain life, or contributes to a patient's death.

The costs and quality adjusted life years associated with each of the levels of harm, as well as the data used to populate the model are described in Section 2.3.

Costs within the analysis were considered from a UK NHS and personal social services perspective, and health outcomes were expressed as quality adjusted life years following the NICE guidelines manual. Due to the short time horizon of the model of less than 1 year (time for prescription to be issued and any errors to materialise) discounting was not carried out. An exception to this was QALY losses associated with severe pADE which occurred over a longer time horizon and were therefore discounted at 3.5% in accordance with the NICE guidelines manual. This is explained in more detail in Section 2.3.5.3.

The population, intervention and comparator were dictated by the randomised control trial (RCT) evidence identified in the clinical effectiveness review. This evidence is described in Section 2.2.

Figure 2.1: Model Structure (Karnon *et al*., 2009)



2.2 EFFECTIVENESS EVIDENCE

Four randomised control trials were identified in the clinical evidence review relating to this topic (section 7). All four RCTs were assessed to see if they were suitable for inclusion within the model. Although evidence on medicine reconciliation in any setting would have been considered provided studies met the inclusion criteria of the review, only evidence relating to medicine reconciliation in a hospital setting was identified.

Bolas *et al*. (2004) compared medicine reconciliation at discharge with usual care and did not report the error rate for the intervention and control groups. In the study the mean mismatch rates between discharge prescription and home medication are provided for the intervention and control group, however this is limited to mismatch between drug name, drug dose and dosage frequency. These are not the same as medication errors and the authors

do not describe them as such. Further, the authors describe that the difference in drug mismatch between the control and intervention group is as a result of prescription lists being faxed to pharmacists for patients randomised to the intervention. Therefore, drug mismatch, and indeed medication errors, resulting from medicine reconciliation are unknown. As a result, the relative risk reduction of medication errors with medicine reconciliation compared with usual care could not be derived from this study.

Nickerson *et al*. (2005) compared medicines reconciliation with usual care and reported the number of drug therapy omissions and inconsistencies for both the intervention and control groups. As for the Bolas paper, it is not clear that this is equivalent to 'medication error'.

Of additional concern was the method used to ascertain inconsistencies and omissions in the intervention and control arms. The intervention involved the pharmacist reviewing a patient's discharge prescription with their drug chart and patient notes. Any discrepancies were then discussed with the patient's hospital physician who had the final say on whether the discrepancy was deliberate or an error. This was logged in the patient notes. Unfortunately no information was provided on whether the discrepancy resulted in a change.

To understand the impact on omissions and inconsistencies of the intervention, pharmacists reviewed all case files in the control group and then a sample in the intervention group after the trial had ended. They reported almost half the patients in the control group had potential inconsistencies or omissions whereas less than 5% did for the intervention. Whilst this seems compelling, unfortunately the figures are not truly comparable as:

- For the control group, the pharmacists did not go back to physicians to check whether perceived errors were deliberate, or not. Therefore, it is not clear how many of the inconsistencies or omissions were actually medication errors or if they were in fact deliberate and thus appropriate for the patient;
- For the intervention group, the patient's notes recorded the physician's final decision (after the pharmacist checked errors with them) meaning even if a potential inconsistency or omission had occurred this would now be recorded as no inconsistency or omission.

This means the true relative risk reduction of medication error from the intervention cannot be calculated – even if omissions and inconsistencies in the study were comparable to medication errors in the model.

Kripalani *et al*. (2012) undertook a RCT comparing clinical pharmacist-led medicine reconciliation at hospital discharge with usual care. In this study usual care involved medicine reconciliation at discharge by the treating physicians and nurses. As such, a relative risk of medication errors resulting from medicine reconciliation could not be established from this study.

Schnipper *et al.* (2009) compared medicine reconciliation at admission and discharge using a computerised medicine reconciliation tool with usual care (no medicine reconciliation). . This study included 322 patients and was carried out in two American hospitals. No

inclusion or exclusion criteria of patients were reported, so it is assumed that all hospitalised patients were eligible for inclusion. The study had a two month follow up period. Full details of this study are provided in the clinical evidence table in Appendix D.1.3. The authors reported the main outcome measure to be unintentional discrepancies between preadmission medications and admission or discharge medications that had the potential for harm. This risk reduction was utilised within the model as described in Section 3.2.3.

Patients within the model received either medicine reconciliation (as defined in Schnipper *et al.* (2009)) or usual care (no medicine reconciliation).

2.3 MODEL INPUTS

2.3.1 Baseline medication error rate

The baseline rate of 1.83 medication errors per patient was taken from McFazean *et al.* (2003) as used and reported by Karnon *et al, (*2009). McFadzean *et al.* undertook a study in a UK medical admissions unit to compare the accuracy of drug history and chart writing of junior doctors and clinical pharmacists. The authors reported prescribing errors and drug chart errors separately and split prescribing errors into errors of omission (omitted drugs), errors of commission (drugs prescribed in error or at the wrong dosage) and errors due to known allergies not being recorded. The baseline prescribing error rate per patient as reported by McFadzean *et al.* is displayed in Table 2.1. More recent UK-based studies of prescribing errors were identified (Franklin *et al*., 2011) and (Vincent *et al*., 2009), however neither provided information that was usable within the model as prescribing errors were not reported by error of omission, error of commission or error due to known allergy.

In the model used by Karnon *et al*. and therefore in the model used within this clinical guideline, medication errors per prescription order rather than medication errors per patient were used. Karnon *et al*. reported the average number of prescriptions per inpatient stay to be 9. This figure was derived from an audit at Royal Hallamshire Hospital, Sheffield, where the mean number of regularly prescribed items was reported to be 8.44 for the hospital population. This was rounded up to 9 to account for 'when required' and single doses (Karnon *et al*., 2009). No range was provided, so a range of 7 to 11 prescription orders per hospitalised patient was assumed to represent NHS hospitals with higher and lower average numbers of prescriptions.

As medicine reconciliation in the RCT conducted by Schnipper *et al.* occurred at both admission and discharge, all medicines prescribed during the hospital stay would be reconciled. Therefore, the rate of errors per prescription order was estimated to be 1.83/9 = 0.203 (0.166 to 0.261). The mean error rate per patient for each of error of omission, error of commission and error due to known allergies was divided by the rate of errors per prescription order from Royal Hallamshire Hospital, Sheffield to derive the error rate per prescription order by type of error. Upper and lower limits were calculated using the assumed range of average prescription orders. This is displayed in Table 2.1.

Table 2.1: Baseline error rate per prescription order

Type of error	Mean error rate (per patient)	Error rate per prescription order		
		Point estimate	Lower limit	Upper limit
Error of omission	1.30	0.26	0.22	0.34
Error of commission	0.53	0.11	0.09	0.14
Error due to known allergies	0.23	0.05	0.04	0.06

2.3.2 Relative risk of error with intervention

A relative risk was applied to each of the error types specified in Section 2.3.1.1. The mean relative risk of 0.72 (95% CI: 0.52-0.99) was taken from Schnipper *et al*. (2009) and describes the reduction in the risk of adverse drug events due to unintentional medical discrepancies resulting from medicine reconciliation. Table 2.2 shows the risk of error by type for the intervention arm of the model.

Table 2.2: Risk of error with medicine reconciliation

Type of error	Mean error rate per prescription order with intervention
Error of omission	0.19
Error of commission	0.08
Error due to known allergies	0.03

2.3.3 Remaining probabilities

The probability of error detection prior to said error reaching the patient for each type of error was taken from Karnon *et al.* who provided estimated ranges of detection rates derived from the literature. The mid-point of each range was utilised in the base case. Both the range of detection rate and the point estimate are shown in Table 2.3. Focused searching did not identify any more recent published literature reporting prescription error detection probabilities by type of error.

Non-detected errors that occur may or may not cause harm to patients. The probabilities of errors causing harm to patients (pADEs) were reported by error type by Karnon *et al*. (2009) (Table 2.3). As with the probability of errors reaching the patient, a range was estimated by Karnon *et al.* using information obtained from the literature (again, no more recent studies were identified). The mid-point of this range has been used in the base case of the model.

Within the model, pADEs were split into being severe (fatal or life threatening); serious; or significant. Within the study by Karnon *et al*., the proportion of each type of pADE was taken from the weighted average of two US studies by Bates and colleagues (1995). An additional, more recent US study was identified (Hug *et al*., 2010) reporting the proportion of pADE by severity in an inpatient population. Hug *et al*. (2010) reported a total of 136

pADEs, of which 35 were significant, 79 serious and 22 fatal or life threatening. No UK based studies reporting the proportion of pADE by type were identified. The NHS Commissioning Board Special Health Authority collects data on patient safety incidents relating to medicines, however the severity of these incidents due to prescribing errors are not reported. Therefore, in the base case the proportions reported by Hug *et al.* were used (displayed in Table 2.3) and sensitivity analysis around these values undertaken. The relevance of using US data to inform the proportion of type of pADEs in the UK is unknown, although it is likely that differences between the settings exist. Estimating the direction and magnitude of these differences is difficult and in doing so may introduce further uncertainty into the model; therefore sensitivity analysis was carried out to assess the impact of changing these values on the results of the model.

Table 2.3: Model input probabilities

	Point estimate	Lower limit	Upper limit
Prescription error detection probabilities			
Error of omission	0.55	0.4	0.7
Error of commission	0.35	0.2	0.5
Error because of known allergies	0.55	0.4	0.7
Probabilities of harm for undetected errors			
Error of omission	0.006	0.001	0.01
Error of commission	0.03	0.01	0.05
Error because of known allergies	0.006	0.001	0.01
Probabilities of type of pADE			
Fatal/life threatening	0.162	0	0.4
Serious	0.581	0	0.82
Significant	0.257	0	0.78

2.3.4 Costs

2.3.4.1 Cost of medicine reconciliation

The medicine reconciliation intervention utilised in the RCT undertaken by Schnipper *et al.* involved reconciliation at both admission and discharge with the assistance of a computer programme. Four components of the intervention were identified: creation of a preadmission medication list (GP-led); use of computer programme; medicine reconciliation at admission (pharmacist-led); and medicine reconciliation at discharge (nurse-led). Resource use was not reported by Schnipper *et al.,* so was determined as accurately as possible from other sources. Table 2.4 provides an overview of the costs and resource use required for this intervention.

The creation of a preadmission medication list is established through taking a medication history from a patient, or their carer. Nester *et al*., 2002 reported the mean time for pharmacists to take medication histories to be 13.4 minutes, with 95% confidence interval (CI) of 11.496 to 15.304 minutes. It was assumed that the length of time required for a GP to take a medication history would be equal to a pharmacist. PSSRU report the cost of a

hospital based doctor (consultant, medical with qualifications) to be £2.32 per minute (PSSRU, 2013). Therefore, the cost of a GP creating a medication list is estimated to be £31.04.

Estimating the cost of the IT programme utilised during medicine reconciliation was more problematic. Karnon *et al*. estimated the cost of a similar programme to be between £1.95 and £7.80 per admission (2005 prices). This cost was estimated based on the lower limit of a cost of setting up (£350,000) and maintaining (£120,000 per year) a Computerised Physician Order Entry System with an assumed 10 year life span. In the current analysis the mid-point of this range was taken and inflated to 2012/13 prices using the PSSRU pay and price index (PSSRU, 2013). This results in an estimated cost of £5.85 per admission.

Karnon *et al*. reported the mean time for pharmacist-led medicine reconciliation to be 22 minutes (95% CI: 12 to 46 minutes). This time includes the time taken to take the patient's medication history. In the intervention by Schnipper *et al*., the medication history is taken by the GP and entered onto the IT programme. Therefore, the time taken for medicine reconciliation without taking the medication history is 22 minus 13.4 minutes, which is equal to 8.6 minutes. The unit cost of a pharmacist per minute with qualifications is £0.78 (PSSRU, 2013). The total cost of pharmacist-led reconciliation at admission is £6.74.

It is reported to take 40 minutes (95% CI: 16.3-103.9) for a nurse to gather a patients medication history and reconcile their medicines. In the intervention reported by Schnipper *et al*., the IT programme in use negates the need for the nurse to take the medication history. Nester *et al*. reported the mean time for a nurse to gather a patient's medication history to be 24.3 minutes (95% CI: 18.673 – 29.927 minutes). Therefore, the time taken for a nurse to reconcile medicines is estimated to be 15.7 minutes. The unit cost of a hospital nurse with qualification costs is £0.68 per minute (PSSRU, 2013). The total cost of nurse-led medicine reconciliation is £10.73.

The total cost of the intervention utilised in the RCT by Schnipper *et al*. can be determined by adding up the costs of all the components of the intervention. This gives a total cost per patient of £54.36. As each patient has a mean of 8.44 prescriptions the intervention cost per prescription order is £6.44. The range of this cost as displayed in Table 2.8 was calculated using the 95% CI for resource utilisation for each intervention component. Sensitivity analysis was conducted using the range of intervention cost.

Table 2.4: Costs and resource use of medicine reconciliation throughout hospital visit

Intervention component	Resource use (mins)	Unit cost	Total cost
Creation of preadmission medication list (GP-led)	13.4	£2.32	£31.04
IT programme utilised during reconciliation	N/A	N/A	£5.85
Pharmacist-led reconciliation at admission	8.6	£0.78	£6.74
Nurse-led medicine reconciliation at discharge	15.7	£0.68	£10.73
Total cost of intervention per patient			**£54.36**
Total cost of intervention per prescription			**£6.04**

All other costs associated with patients undergoing medicine reconciliation were assumed to be equal to usual care and were therefore not included within the model.

2.3.4.2 Cost of medication errors

The cost of pADE were taken from Karnon *et al*. and inflated to 2012/13 prices using the PSSRU pay and price index. These are displayed in Table 2.5. For each cost a range was reported and utilised in both deterministic and probabilistic sensitivity analysis. A description of the implications of severity of medication errors is provided in Section 2.1 and further information on the derivation of costs provided subsequently.

Many of the sources used to determine resource usage and therefore costs were US sources which may have limited applicability to the NHS, hence Karnon *et al.* (2009) provided a range of costs. The cost of detecting a medication error prior to it reaching the patients was based on an estimated cost by the Leapfrog group (as US agency attempting to improve safety in hospitals). A cost may be incurred when detecting a medical error due to the time spent working out if an error has occurred; however, this is not always the case and the range provided by the Leapfrog group included a £0 estimate. The cost of a significant pADE (an error that did not have any impact on length of stay in hospital) was taken from a US study which estimated amongst other things the cost of medication errors that required extra laboratory tests or treatment without extending length of stay (Schneider *et al*., 1995).

This cost was combined with additional length of stay to calculate the cost of a serious pADE. Additional length of stay was reported to range between 4.6 (Bates *et al.,*1997) and 7 days (Pinilla *et al*.,2006) which was multiplied by the mean cost of a day spent on a non-ICU ward (from NHS reference costs) by Karnon *et al*., 2009. For a severe pADE additional length of stay had a range of 7 to 10 days (Pinilla *et al*., 2006) and again was multiplied by the mean cost of a day spent on a non-ICU ward (Karnon *et al.*, 2009). The costs used by Karnon *et al*. have been inflated to 2012/13 prices and are displayed in Table 2.5.

Table 2.5: Cost of medication errors

Type of medication error	Point estimate	Lower limit	Upper limit
Medication error detected prior to reaching patient	£3.60	£0	£7.20
Significant pADE (no increase in length of stay)	£129	£78.01	£180.01
Serious pADE	£1,316	£855.66	£1,780.92
Severe (life threatening or fatal) pADE	£1,923	£1,302.09	£2,544.18

2.3.5 Utilities

In the analysis by Karnon *et al*., which the current analysis aimed to update, pADE were split into three levels of severity. Significant pADEs resulted in temporary harm to patients and required intervention (with no increase in hospital length of stay). Serious pADEs also resulted in temporary harm to the patient, but required initial or prolonged hospitalisations. Severe pADEs were life threatening or fatal and resulted in either permanent patient harm, intervention to sustain life, or contributed to a patient's death (Karnon *et al*., 2009).

The QALY losses due to pADEs were estimated by Karnon *et al.* using two methods. Firstly, a crude estimate of QALYs lost per pADE was obtained through analysing NHS litigation payments and using the NICE implied range of a value of a QALY of between £20,000 and £30,000 to calculate the QALY loss experienced through adverse health consequence resulting from health service error. Second, Karnon *et al*., attempted to value QALY effects of ADEs by assuming a utility decrement for each category of ADE and combining this with the duration of adverse effects to obtain a QALY loss. As this part of the analysis undertaken by Karnon *et al*. was based upon assumptions rather than published data, a literature review was undertaken to identify any studies providing more robust utility data.

2.3.5.1 Eligibility criteria

The eligibility criteria used to identify and select utilities studies are detailed below.

1) Participants:
   - Eligible studies included patients taking medicines who experienced adverse drug events.
2) Study types:
   - Reports of utility elicitation exercises;
   - Reports of utility validation exercises;
   - Reports of economic evaluations using utility measures;
   - Reviews of utility studies (which were unpicked in order to harvest any relevant studies);
   - Unpublished studies or conference abstracts were suitable for inclusion.

2.3.5.2 Search strategy

A pragmatic, focused literature search was designed to identify studies with utility values for adverse drug events in hospitalised patients. The strategy comprised 3 main concepts: hospitalisation, adverse drug events and utilities. The concepts were structured as follows:

hospitalisation AND adverse drug events AND utilities

To increase search sensitivity in relation to studies on adverse drug events caused by medication errors, a highly focused set of medication error terms was also combined as AND with the utilities concept only.

The strategy was developed for MEDLINE (Ovid interface). The search strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and keyword heading word fields. The search terms were identified through discussion between the research team, by scanning background literature, and by browsing database thesauri. The strategy excluded some publication types which are unlikely to yield relevant reports: letters, editorials, comments, news. The strategy also excluded animal studies. The searches were limited to English language studies only, and to records added to the database since 2007, using appropriate fields such as the entry date field in MEDLINE. The start of 2007 was identified by the research team as an appropriate cut-off date as Karnon *et al.*, (2009) undertook their searches in June 2007. Therefore, it was assumed that any relevant studies published prior to 2007 would have been captured by Karnon *et al*. When developing the strategy a number of pragmatic search decisions were taken following discussion within the research team to ensure a balance between search sensitivity and precision which was appropriate to the project time-frame.

The MEDLINE strategy was translated appropriately for other databases. Where database functionality did not allow limiting by record entry date, results were limited to records of publications with a publication date of 2007 to date. The full search strategies (including search dates) are included in Appendix A.

Searches were carried out in a range of relevant search sources. The databases and information sources searched are shown in Table 2.6.

Table 2.6: Databases and information sources searched

Database / information source	Interface / URL
MEDLINE and MEDLINE In-Process	OvidSP
EMBASE	OvidSP
EconLit	OvidSP
NHS Economic Evaluation Database (NHS EED)	Cochrane Library/Wiley Interscience
Health Economic Evaluation Database (HEED)	EBSCOHOST
Cost-Effectiveness Analysis (CEA) Registry	https://research.tufts-nemc.org/cear4/Home.aspx
Health Technology Assessment Database (HTA Database)	Cochrane Library/Wiley Interscience
ScHARRHUD	http://update-sbs.update.co.uk/scharr11/index.php?recordsN1&m=search

Searching a number of databases produces a degree of duplication in the results. To manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into EndNote bibliographic management software and duplicate records were removed using several algorithms.

2.3.5.3 Results

The searches identified 4,453 records (Table 2.7). Following deduplication 3,513 records were assessed for relevance.

Table 2.7: Number of search records identified

Resource	Records identified
MEDLINE and MEDLINE In-Process	1276
EMBASE	2029
EconLit	9
NHS Economic Evaluation Database (NHS EED)	900
Health Economic Evaluation Database (HEED)	144
Cost-Effectiveness Analysis (CEA) Registry	1
Health Technology Assessment Database (HTA Database)	55
ScHARRHUD (Health Utilities Database)	39
TOTAL	**4453**
TOTAL after deduplication	**3513**

The titles and abstracts of the 3,513 unique search records were screened against the eligibility criteria and 3,477 records were excluded. The full papers of the remaining 36 studies were considered and three studies were identified as meeting the inclusion criteria. A PRISMA diagram showing how the records were processed following the searches is displayed in Figure 2.2. A full list of the studies excluded at the full paper review stage and their reason for exclusion is displayed in Appendix B.

Three studies met the inclusion criteria by reporting utility values of patients experiencing adverse drug events. Rattanvipapong *et al*. (2013) undertook an economic evaluation in Thailand of screening for carbamazepine-induced severe adverse drug reactions with utility measures reported directly from patients. Utility scores were provided for patients with Stevens-Johnson syndrome and toxic epidermal necrolysis – acquired bullous disorders of the skin that can be adverse reactions to carbamazepine. Utility scores for patients developing these adverse reactions were -0.08 for patients with epilepsy and -0.18 for patients with neuropathic pain. The mean utility score for patients with epilepsy was 0.68 and for neuropathic pain 0.63. The adverse drug events considered within this study were specific to a particular drug and only applicable to patients with newly diagnosed epilepsy or neuropathic pain; as such, the paper was judged to be not generalisable to patient population in this economic model (all hospitalised patients). Further, utility values were only provided for a specific severe pADE and no utility values were provided for either significant or serious pADEs.

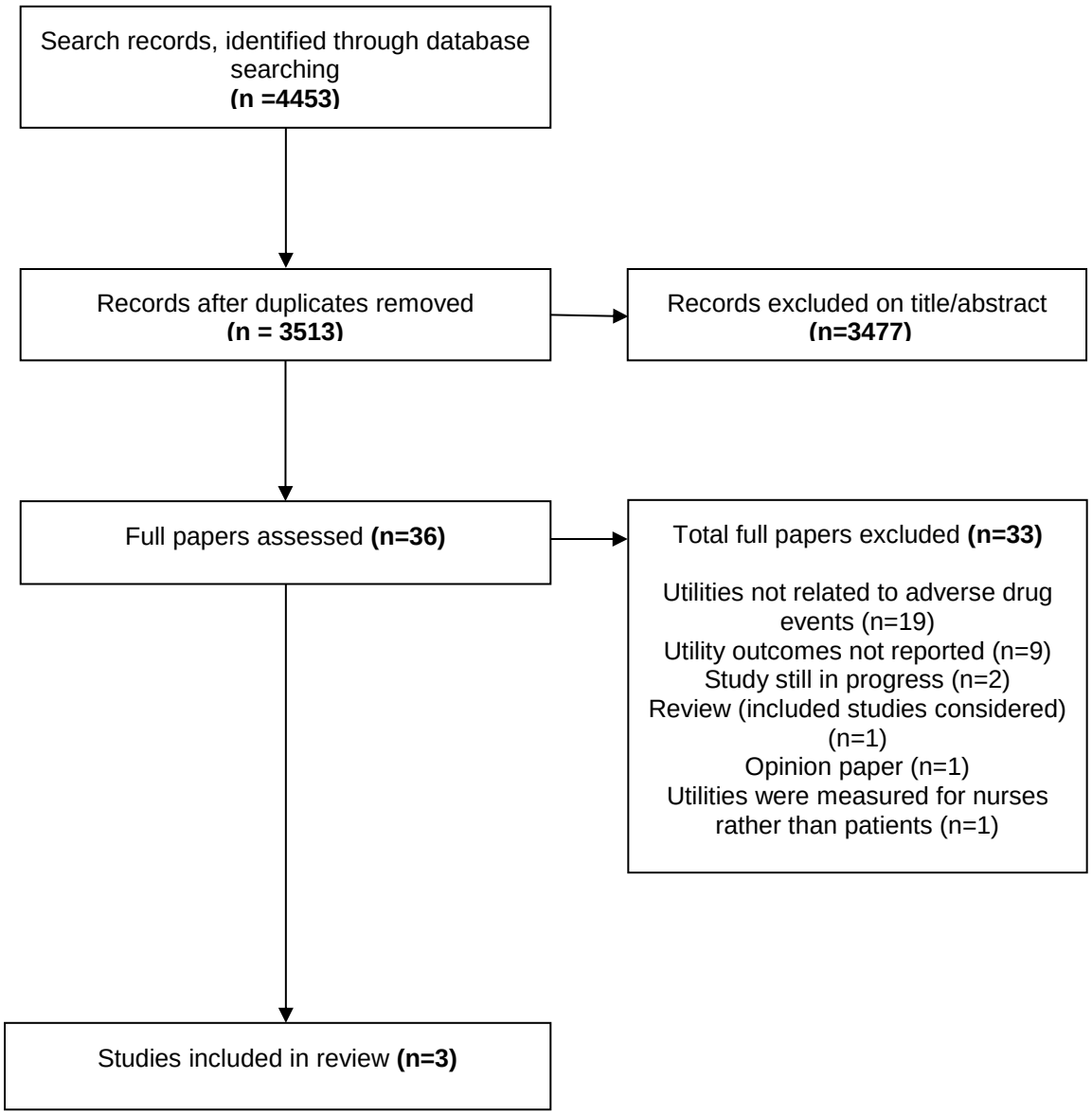
The two remaining papers were both by Karnon, and included Karnon *et al.* (2009) on which this model is based. The utilities provided in each of these two papers related to adverse drug events in hospitalised patients, as required for this economic model (given the model was based on that constructed by Karnon *et al*.). In both studies utility estimates were derived from assumptions rather than being elicited from patients themselves. In Karnon *et al.* (2008) utility values were estimated though an analysis of NHS litigation payments as described in Section 2.3.3. In the 2009 paper, both this method and estimations of QALY loss based upon expert opinion were utilised. Both papers have limited validity, however

given that the 2009 elicited utilities via two methods, this study was deemed to be slightly more robust.

Karnon *et al.* (2009) provided ranges for the QALY loss associated with significant, serious and severe pADEs (as described in Section 2.1). The ranges provided were calculated though two difference methods. Firstly, data from NHS litigation payments for patients experiencing adverse health consequences resulting from health care system error were considered. The litigation payments were analysed to provide a crude estimate of QALYs lost per ADE using the NICE implied threshold value of a QALY of between £20,000 and £30,000. Payments were put in order and ranges for each severity of ADE determined. Secondly, QALY effects were described directly by determining the utility decrement and time frame of this utility decrement resulting from an ADE. Estimated utility losses were determined by Karnon *et al*. In order to calculate QALY losses, Karnon *et al*. (2009) considered utility losses over a certain time frame dependent on the severity of the pADE. For significant and serious pADE utility losses were judged to have a short duration of less than one year. Severe pADE had a longer duration and Karnon et al. discounted the QALY losses associated with these to account for time preferences at a rate of 3.5% per year consistent with the NICE guidelines manual.

The values used within the model taken from Karnon *et al.* (2009) are displayed in Table 2.8. In the base case, the mid-point of each of these ranges was used. Extensive sensitivity analysis was undertaken around the QALY loss for each degree of pADE in order to determine the importance of the uncertainty of these values.

Figure 2.2: PRISMA flow diagram



2.3.6 Summary of model inputs

Table 2.8 provides an overview of all input parameters used within the model. The range for each input and the distribution of that range is also provided. The ranges around point estimates were used within deterministic and probabilistic sensitivity analyses (PSA).

Table 2.8: Summary of model inputs

Parameter	Point estimate	Probability distribution and Alpha where applicable	Distribution range[1]	Source
Relative risk with intervention	0.72	Lognormal	0.52-0.99	Schnipper (2009)
Baseline risk of error of omission	0.26	Uniform	0.22-0.34	Karnon (2009) and McFadzean (2003)
Baseline risk of error of commission	0.11	Uniform	0.09-0.14	Karnon (2009) and McFadzean (2003)
Baseline risk of error due to known allergy	0.05	Uniform	0.04-0.06	Karnon (2009) and McFadzean (2003)
Probability of error detection – error of omission	0.55	Uniform	0.4-0.7	Karnon (2009)
Probability of error detection – error of commission	0.35	Uniform	0.2-0.5	Karnon (2009)
Probability of error detection – error due to known allergy	0.55	Uniform	0.4-0.7	Karnon (2009)
Probability of harm from error of omission	0.006	Uniform	0.001-0.01	Karnon (2009)
Probability of harm from error of commission	0.03	Uniform	0.01-0.05	Karnon (2009)
Probability of harm from error due to known allergy	0.006	Uniform	0.001-0.01	Karnon (2009)
Proportion of severe pADE	0.162[1,2]	Dirichlet (Alpha = 22)	0-0.4	Hug (2010). Range assumed
Proportion of serious pADE	0.581[1,2]	Dirichlet (Alpha = 79)	0-0.82	Hug (2010). Range assumed
Proportion of significant pADE	0.257[1,2]	Dirichlet (Alpha = 35)	0-0.39	Hug (2010). Range assumed
Cost of medicine reconciliation per patient	£54.36	Gamma	£36 - £124	See section 2.3.2.1
Cost of detected medication error	£3.60	Uniform	£0-£7.20	See section 2.3.2.2
Cost of significant pADE	£129	Uniform	£78.01-£180.01	See section 2.3.2.2
Cost of serious pADE	£1,316	Uniform	£855.66-£1,780.92	See section 2.3.2.2
Cost of severe pADE	£1,923	Uniform	£1,302.09-£2,544.18	See section 2.3.2.2
QALY loss from significant pADE	0.0045	Uniform	0.001-0.008	Karnon (2009).
QALY loss from serious pADE	0.0755	Uniform	0.061-0.09	Karnon (2009).
QALY loss from severe pADE	2.705	Uniform	1-4.41	Karnon (2009).

[1] The distribution range was used in both deterministic and probabilistic sensitivity analysis, with the exception of the proportion of type of pADE where the range provided was used for deterministic analysis only. Probabilistic sensitivity analysis for this variable used Deirichlet distribution (Briggs et al, 2006).

[2] During deterministic sensitivity analysis it was assumed that an increase in any type of pADE was complimented by a decrease in the number of patients experiencing no harm from medication errors.

2.4 SENSITVITY ANALYSIS

Deterministic and probabilistic sensitivity analyses were undertaken using the ranges and distributions displayed in Table 2.8. Given the lack of available data, extensive sensitivity analyses were carried out, which included univariate sensitivity analyses (varying one input at a time) around all model inputs and two-way sensitivity analyses (varying two inputs at a time) around the following inputs:

- Relative risk reduction of medication errors with medicine reconciliation and cost of medicine reconciliation;
- Proportion and cost of significant pADE;
- Proportion and cost of serious pADE;
- Proportion and cost of severe pADE;
- Proportion and QALY loss of significant pADE;
- Proportion and QALY loss of serious pADE;
- Proportion and QALY loss of severe pADE.

In addition, a probabilistic approach was also undertaken whereby the key inputs to the model were each selected from a distribution, rather than using one fixed value for each input. The model is run 10,000 times, each iteration using a different set of values for the inputs. The ICER from each iteration is collected and the spread can be examined. This can provide information on the level of certainty of results in the model. If the ICERs from of all of the iterations are very tightly clustered together, this indicates that the results of the model do not change greatly when the inputs are varied within plausible ranges. PSA provides information on the level of certainty of *direction* of results of the model, i.e. whether medicine reconciliation is or is not cost-effective. The spread of results displays the proportion of iterations in which the ICER was below the threshold and, therefore, in what proportion of iterations the new technology was estimated to be cost-effective.

To generate the input values for each iteration, distributions were fitted to key parameters within the model. Uniform distributions were used for many of the input parameters, as the only data available were ranges and medians. Cost parameters (where confidence intervals for resources use were available) were fitted with gamma distributions which produce only non-negative values. For relative risk the lognormal distribution was used.

The results of both deterministic and PSA are reported in Sections 3.2 and 3.3.

2.5 MODEL VALIDATION

As this analysis aimed to update the analysis undertaken by Karnon *et al.* the model structure was identical to that in the study. The analysis by Karnon and colleagues underwent peer review during the publication process. The current evaluation was carried out in consultation with the GDG, who discussed the validity of the model structure, inputs and results.

The model was checked by the two health economists involved in building the model and the results critiqued for plausibility. A third health economist within YHEC who had not been involved in building the model peer reviewed and 'pressure tested' the model.

Section 3: Results

3.1 BASE CASE RESULTS

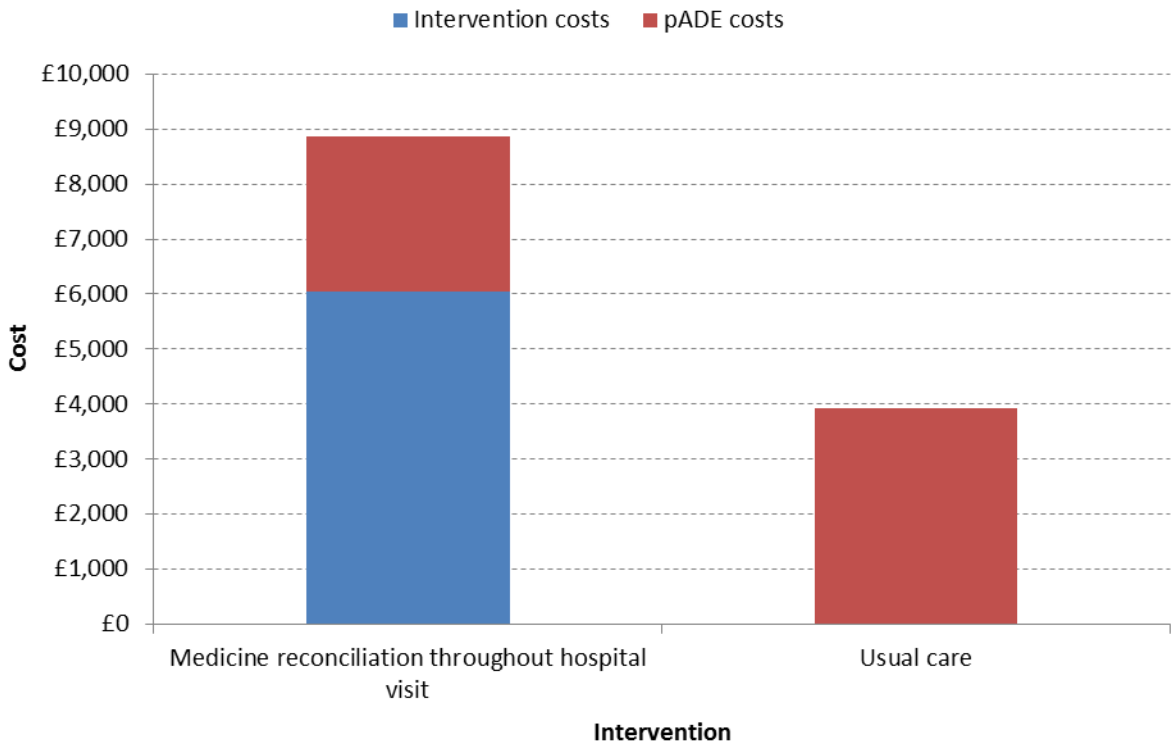
The base case results show that compared with usual care, medicine reconciliation throughout a hospital stay has a deterministic incremental cost per QALY of £12,726 and a probabilistic incremental cost per QALY of £18,085. The base case results are displayed in Tables 3.1.

Table 3.1: Base case results

	Medicine reconciliation	**Usual care**
Intervention cost	£6,040	£0
pADE cost	£2,834	£3,936
Total cost (per 1000 prescription orders)	**£8,874**	**£3,936**
QALY loss (per 1000 prescription orders)	**-1.00**	**-1.39**
Incremental cost (per 1000 prescription orders)		£4,938
Incremental QALY gain (per 1000 prescription orders)		0.39
Deterministic Incremental cost per QALY		**£12,726**
Deterministic Net benefit (with threshold of £20,000)		**£2,822**
Deterministic Net benefit (with threshold of £30,000)		**£6,702**
Probabilistic Incremental cost per QALY		**£18,085**

A breakdown of costs is displayed in Figure 3.1 to show the costs attributable to the intervention and to pADEs for both medicine reconciliation and usual care. In the base case, the overall cost of medicine reconciliation is greater than usual care; however, the costs due to pADEs with medicine reconciliation are lower than with usual care.

Figure 3.1: Cost breakdown



3.2 DETERMINSTIC SENSITIVITY ANALYSIS

3.2.1 Univariate analysis

Univariate sensitivity analysis was undertaken around all model inputs to determine the key variables that had the largest impact on the results of the model. Sensitivity analysis around the following parameters within the ranges specified in Table 2.8 resulted in the net benefit (at a threshold of £20,000) to be negative, meaning medicine reconciliation was no longer cost-effective compared with usual care:

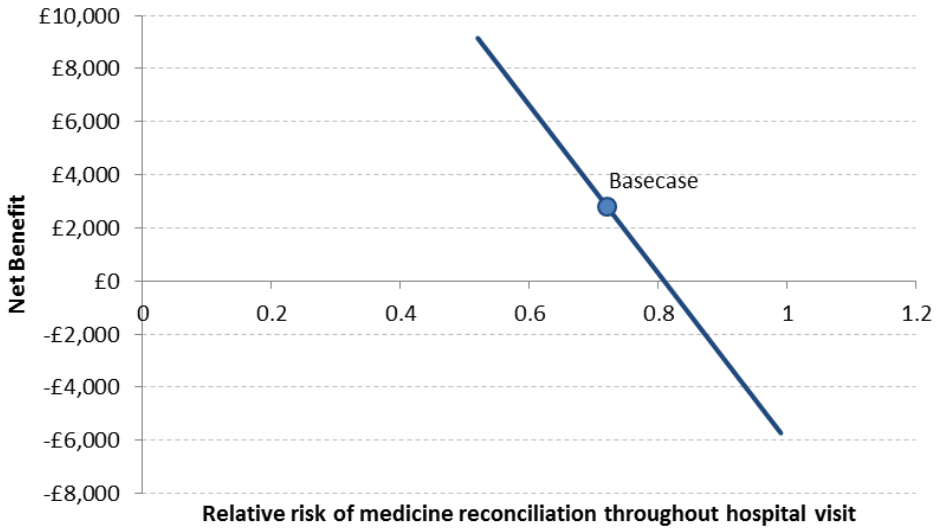
- Relative risk of medication errors with medicine reconciliation;
- Baseline probability of error of commission;
- Probability of harm after error of commission;
- Probability of type of pADE (severe, serious of significant);
- Cost of medicine reconciliation;
- QALY loss per severe pADE.

For all other parameters, medicine reconciliation remained cost-effective when varied within the specified range. The results of the one-way sensitivity analysis around each of input parameters listed above are now described in more detail. The graphs for the remaining univariate sensitivity analysis results are provided in Appendix C.

3.2.1.1 Relative risk of medicine errors with medicine reconciliation

Figure 3.2 shows how a change in the relative risk of reconciliation medication error resulting from medicine reconciliation impacts upon net benefit. Within the model the relative risk is applied to the baseline probabilities of error to derive the probabilities of error with medicine reconciliation. Where the relative risk of medicine error with medicine reconciliation is above 0.81, medicine reconciliation is no longer cost effective at a £20,000 per QALY threshold. Schnipper *et al.*, reported that the mean relative risk to be 0.72 with a 95% CI of 0.52 to 0.99.

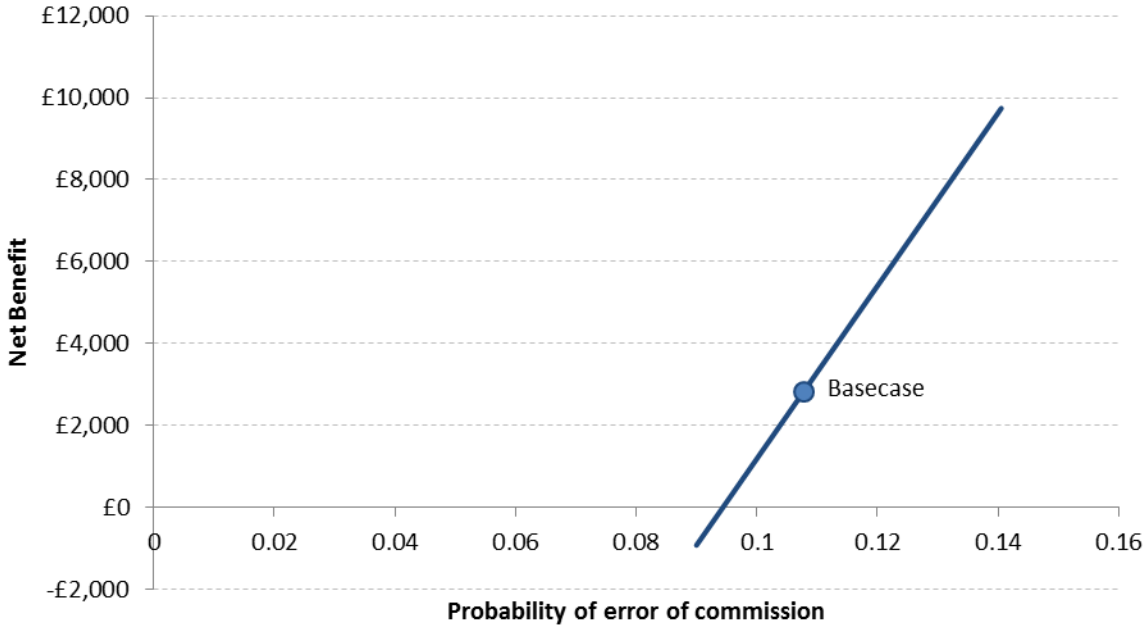
Figure 3.2: Univariate sensitivity analysis – relative risk with medicine reconciliation



3.2.1.2 Baseline probability of error of commission

The impact of a change in the baseline probability of an error of commission is displayed in Figure 3.3. This shows that where the baseline error of commission probability (i.e. the probability of an error of commission in usual care) is below 0.0945 medicine reconciliation no longer generated a net benefit compared to usual care. The reason for this is that if fewer errors occur, then there is less scope for error reduction as a result of medicine reconciliation. The lower boundary of the 95% CI reported in the literature was 0.089 (McFadzean *et al*., 2003).

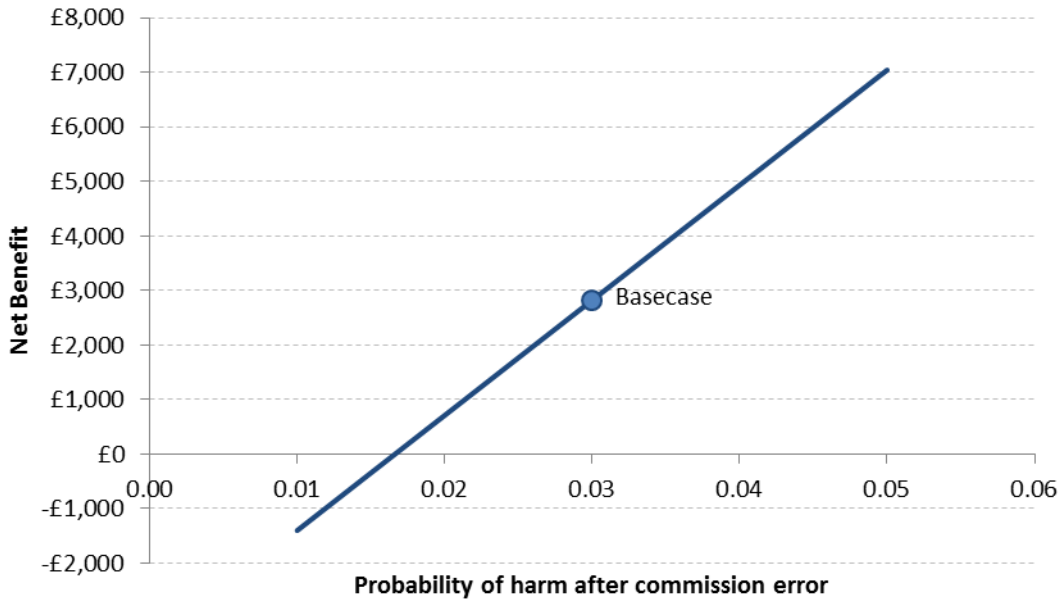
Figure 3.3: Univariate sensitivity analysis – baseline probability of error of commission



3.2.1.3 Probability of harm following undetected error of commission

Where the probability of harm resulting from an undetected error of commission is very low, the net benefit of medicine reconciliation is negative, i.e. medicine reconciliation is no longer cost-effective versus usual care. Figure 3.4 shows that where the probability of harm is below 0.017, medicine reconciliation is no longer cost-effective. Karnon *et al*. reported the range of probability of harm following an undetected error to be between 0.001 and 0.05 (Karnon *et al.*, 2009). Where harm does not occur following an error, the QALY loss and costs associated with errors are not experienced. The lower the probability of harm occurring in usual care, the less scope there is for medicine reconciliation to improve outcomes by ensuring that errors do not occur.

Figure 3.4: Univariate sensitivity analysis – probability of harm following undetected error of commission



3.2.1.4 Proportion of type of pADE

Within the base case of the economic model the proportion of each type of pADE (significant, serious or severe) were correlated in that as proportions they always had to sum to one. When deterministic sensitivity analysis was undertaken around these values, an increase in the proportion of any type of pADE resulted in a decrease of the number of patients experiencing no harm from a medication error. As such, if the proportion of severe pADE increased, more patients went down the 'error causes harm' arm of the decision tree rather than the 'error causes no harm' arm. Likewise, if the proportion of patients experiencing pADEs reduced, the number of patients in the 'error causes no harm' arm increased.

Figure 3.5 displays sensitivity analysis conducted around each of the types of pADE. No ranges to consider were identified in the literature, so a wide range for each parameter was considered to test the effect on the model's results.

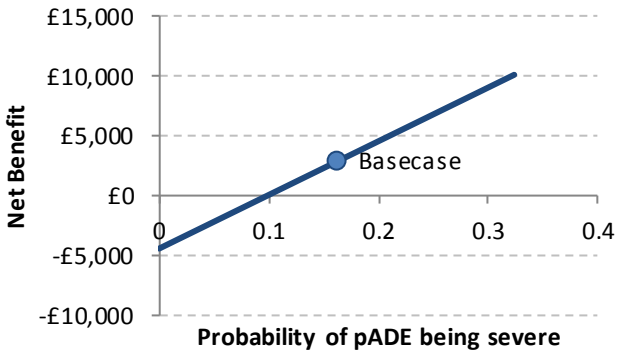
The graphs show that as the probability of each type of pADEs falls, the net benefit falls as a lower number of pADE decreases the scope of improvement available for medicine reconciliation. The graph is steepest for severe pADEs meaning that a change in the proportion of severe pADEs has a larger impact on the results of the model than a change in serious or significant pADEs. This occurs because a severe pADE evokes a greater cost and greater QALY loss than the other two types of pADEs.

Of the three graphs displayed in Figure 3.5, only in the severe pADE does a change in the proportion of pADE result in a negative net benefit with medicine reconciliation. This occurs

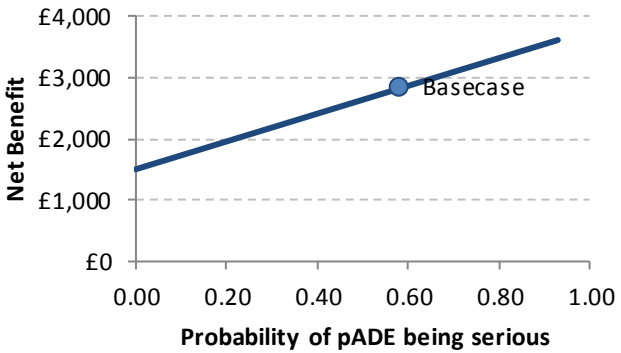
where the proportion of severe pADEs is less than 10%. Hug *et al.,* reported the proportion of severe pADEs to be 16% as used in the base case (Hug *et al*., 2010). A weighted average of the results from two older studies by Bates et al. was used by Karnon, who reported 20% of pADEs to be severe, 41% serious and 39% significant (Karnon *et al*., 2009). Therefore, these results suggest that the proportion of severe pADEs is above 10.5%; indeed, this was found to be 20% in both Bates *et al.*, (1995a) and Bates *et al*., (1995b). Inputting the weighted averages from the studies by Bates into this model generates an ICER of £10,939 (lower than the base case ICER of £12,726). As no UK data was identified, it is difficult to determine whether or not the proportion of severe pADEs is above 10.5% in a UK NHS setting.

Figure 3.5: Sensitivity analysis around the percentage of type of pADE

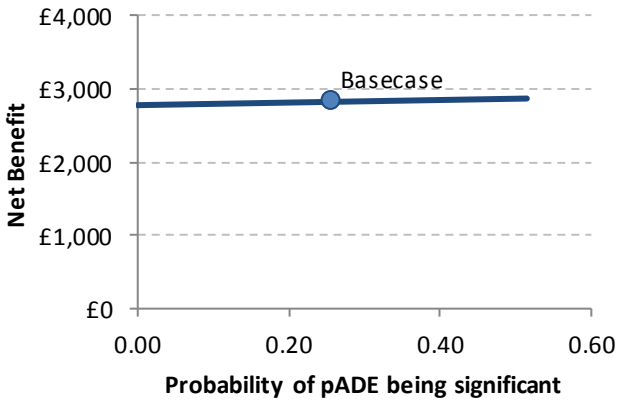
Severe pADE



Serious pADE



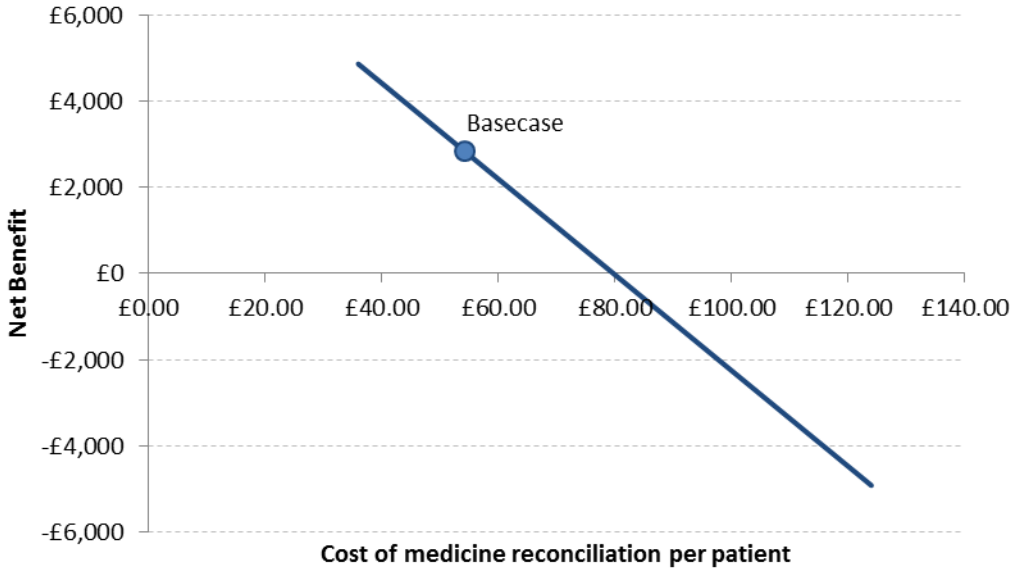
Significant pADE



3.2.1.5 Cost of medicine reconciliation

Figure 3.6 shows how the cost of medicine reconciliation per patient impacts upon the results of the model. Where the cost is above £79.75 per patient, medicine reconciliation no longer generates a net benefit.

Figure 3.6: Univariate sensitivity analysis – cost of medicine reconciliation



Calculation of the cost of medicine reconciliation throughout the hospital visit, as described by Schnipper *et al.* involved making assumptions (using other sources) around the resource use involved, as this was not reported within the RCT. In order for the cost of medicine reconciliation throughout the hospital visit to be above £79, the cost of creation of preadmission medication list, pharmacist-led reconciliation at admission and nurse-led reconciliation at discharge must cost more than £73 (as IT system has an estimated cost of around £6). Various permutations of the time that must be involved for the three components in order to generate a cost of £73 are displayed in Table 3.2.

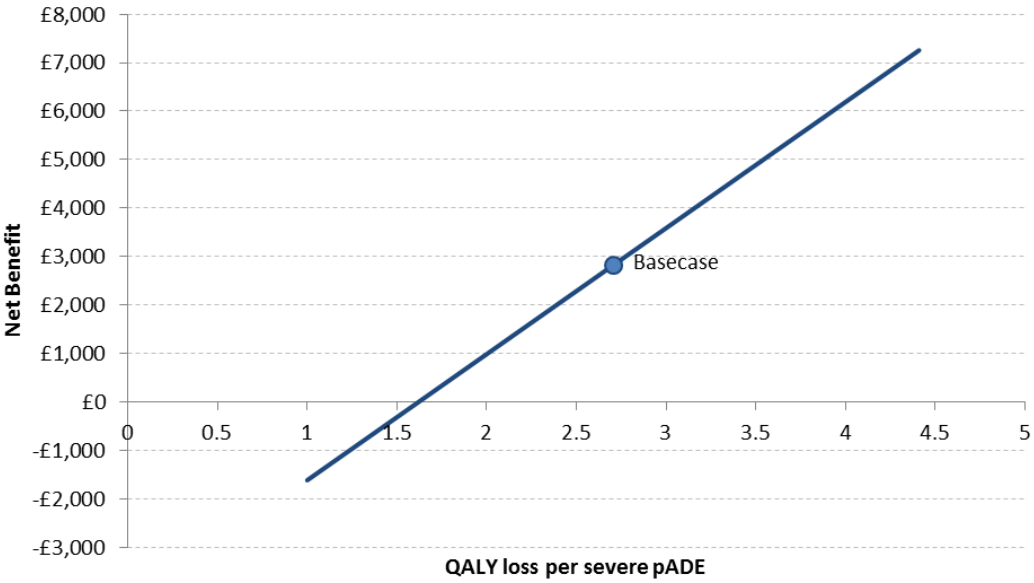
Table 3.2: Examples of permutations of healthcare profession resource use

Task	Time			
	Example 1	**Example 2**	**Example 3**	**Example 4**
Generation of pre-admission medication list and put onto IT programme (GP led)	8 mins	12 mins	16 mins	20 mins
Medicine reconciliation at admission (pharmacist-led)	38 mins	30 mins	20 mins	15 mins
Medicine reconciliation at discharge (nurse-led)	36 mins	32 mins	29 mins	22 mins

3.2.1.6 QALY loss for a severe pADE

The QALY loss associated with a severe pADE was varied between 1 and 4.41 QALYs. As shown in Figure 3.7 where the QALY loss from a severe pADE (fatal or life threatening) was less than 1.62 QALYs, medicine reconciliation no longer generated a net benefit. Where the QALY loss from a severe pADE is smaller, the benefits of avoiding severe events are reduced and consequently the value of medicine reconciliation which aims to reduce pADEs is also reduced. A QALY is equal to full health for one year, or 50% health for two years, or indeed any permutation of two numbers that multiply together to give the answer one. Therefore a QALY loss of 1.62 is the equivalent, for example, of an individual's utility being reduced by 0.162 for 10 years. There are of course many permutations of utility decrements and time spans that can be multiplied together to generate a QALY loss of 1.62. Varying the QALY loss associated with serious or significant pADEs within the ranges specified in Section 2 did not change the direction of the results.

Figure 3.7: Univariate sensitivity analysis – QALY loss associated with severe pADE



3.2.2 Tornado diagram

The tornado diagram displayed in Figure 3.8 provides an overview of the impact on the results of the model depending on the input parameter being varied. The ranges used for each input are those specified in Table 2.8, the rationale for which are provided in Section 2. For all input parameter ranges were taken from information in the literature, with the exception of the proportion of each type of pADE which were assumed. It is clear from this diagram that the key driver of the model is the relative risk with medicine reconciliation. The impact on the ICER when this input parameter is varied within the 95% confidence interval as reported in the RCT (Schnipper *et al.*, 2009) is large. The effect of varying the proportion of severe pADEs also has a large impact on the ICER, however, it is important to note that

for this variable the range considered was assumed and purposely large in order to assess its influence on the results.

Figure 3.8: Tornado diagram

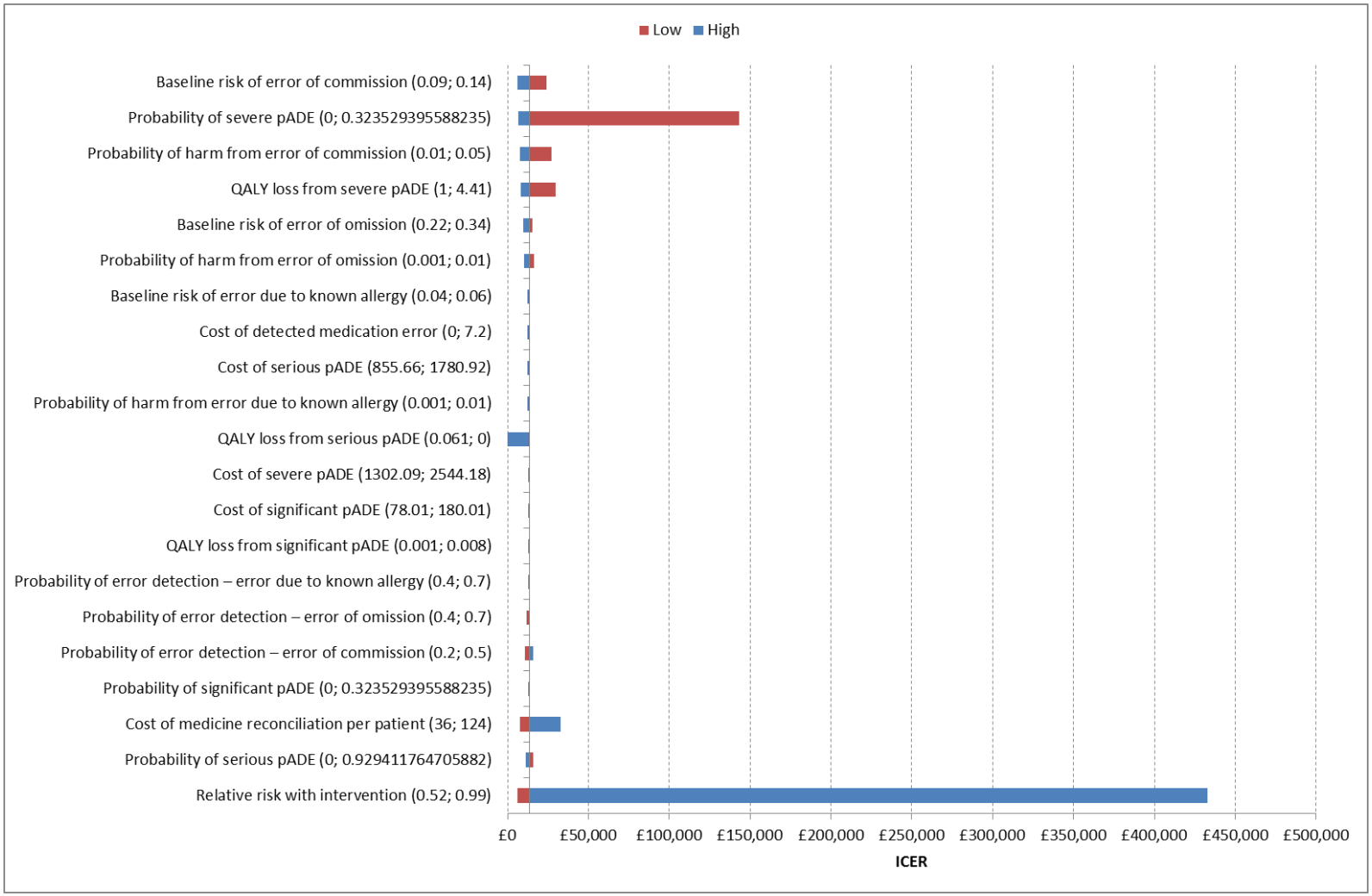


Figure 3.9: Tornado diagram with relative risk of intervention and proportion of severe pADEs removed

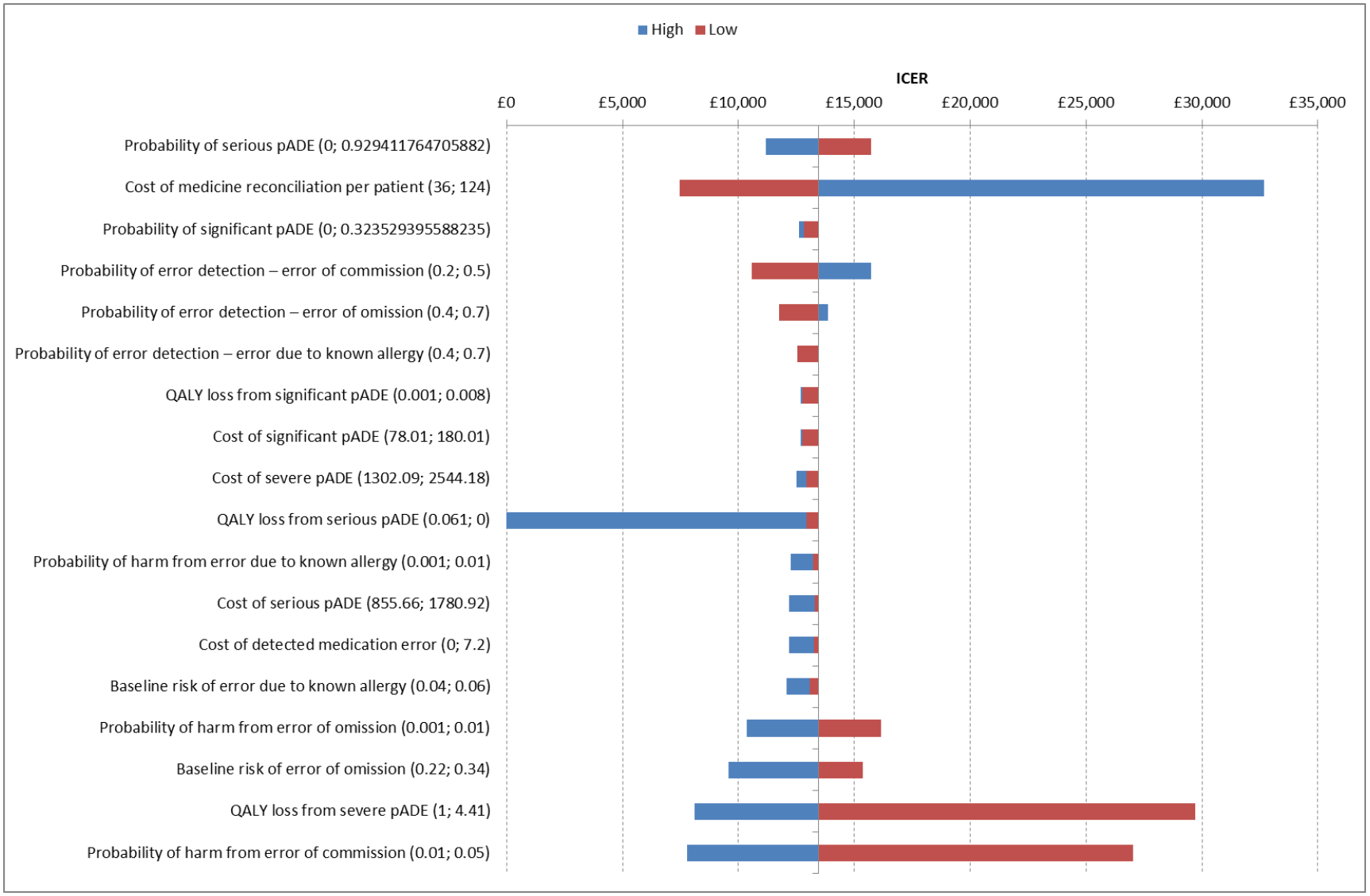


Figure 3.9 shows a tornado diagram with the two key variables mentioned previously removed. This enables the reader to assess more easily the relative impact of the other model input parameters.

3.2.3 Threshold analysis

Table 3.3 summarises the results of the univariate sensitivity analysis by showing the minimum or maximum parameter value required for the intervention to be considered cost-effective at both a £20,000 and £30,000 threshold. The model parameters considered are those specified in Table 2.8. Threshold analysis can provide insight into the most extreme value that an input parameter can take, whilst the medicine reconciliation intervention remains cost-effective. For example, at a £20,000 threshold medicine reconciliation will be cost effective provided the cost of medicine reconciliation is less than £79.75 per person. Similarly, at the £30,000 threshold medicine reconciliation will be cost effective provided the cost of medicine reconciliation is less than £114.67 per person.

As evident from the results shown in Table 3.3, some input parameters have little impact upon the results of the model, such that even when these inputs reach the most extreme value possible, the overall result is that medicine reconciliation is cost-effective. Such inputs are baseline risk of error due to known allergy; probability of error detection (error of omission and error due to known allergy); probability of harm from an error (error of omission and error due to known allergy); proportion of serious and significant pADEs; cost of detected medication error; cost of all types of pADE and QALY losses from serious and significant pADEs. These inputs when varied individually have little impact on the overall results of the model.

The remaining model inputs have a greater impact upon the results of the model. These inputs include the key drivers of the model as identified in Section 3.2.2. Table 3.3 specifies that at a £20,000 threshold medicine reconciliation will be cost effective provided the relative risk of medication errors is 0.81 or below. Similarly, at the £30,000 threshold medicine reconciliation will be cost effective provided the relative risk of medication errors is 0.86 or below. Further, in order for medicine reconciliation to be cost effective at a £20,000 threshold at least 10% of pADE must be severe and at a £30,000 threshold at least 6.1% of pADE must be severe.

Table 3.3: Threshold values of input parameters

Parameter	Point estimate used in base case	Maximum/minimum to be cost-effective at £20,000 threshold	Maximum/minimum to be cost-effective at £30,000 threshold
Relative risk with intervention	0.72	Maximum of 0.81	Maximum of 0.86
Baseline risk of error of omission	0.26	Minimum of 0.17	Minimum of 0.1
Baseline risk of error of commission	0.11	Minimum of 0.0945	Minimum of 0.086
Baseline risk of error due to known allergy	0.05	Intervention is cost-effective where this equals 0	Intervention is cost-effective where this equals 0
Probability of error detection – error of omission	0.55	Intervention is cost-effective where this equals 1	Intervention is cost-effective where this equals 1
Probability of error detection – error of commission	0.35	Maximum of 0.64	Maximum of 0.82
Probability of error detection – error due to known allergy	0.55	Intervention is cost-effective where this equals 1	Intervention is cost-effective where this equals 1
Probability of harm from error of omission	0.006	Intervention is cost-effective where this equals 0	Intervention is cost-effective where this equals 0
Probability of harm from error of commission	0.03	Minimum of 0.017	Minimum of 0.0085
Probability of harm from error due to known allergy	0.006	Intervention is cost-effective where this equals 0	Intervention is cost-effective where this equals 0
Proportion of severe pADE	0.2	Minimum of 0.1	Minimum of 0.061
Proportion of serious pADE	0.41	Intervention is cost-effective where this equals 0	Intervention is cost-effective where this equals 0
Proportion of significant pADE	0.39	Intervention is cost-effective where this equals 0	Intervention is cost-effective where this equals 0
Cost of medicine reconciliation per patient	£54.36	Maximum of £79.75	Maximum of £114.67
Cost of detected medication error	£3.60	Intervention is cost-effective where this equals £0	Intervention is cost-effective where this equals £0
Cost of significant pADE	£129	Intervention is cost-effective where this equals £0	Intervention is cost-effective where this equals £0
Cost of serious pADE	£1,316	Intervention is cost-effective where this equals £0	Intervention is cost-effective where this equals £0
Cost of severe pADE	£1,923	Intervention is cost-effective where this equals £0	Intervention is cost-effective where this equals £0
QALY loss from significant pADE	0.0045	Intervention is cost-effective where this equals 0	Intervention is cost-effective where this equals 0
QALY loss from serious pADE	0.0755	Intervention is cost-effective where this equals 0	Intervention is cost-effective where this equals 0
QALY loss from severe pADE	2.705	Minimum of 1.62 QALYs lost	Minimum of 0.988 QALYs lost

3.2.4 Two-way sensitivity analysis

Two-way sensitivity analysis involves varying two input parameters together to assess the impact upon the model results. The combinations of two-way sensitivity analysis that were carried out are provided in Section 2.4. The results are reported here for two of the two-way analyses carried out. For the remaining analyses the two-way sensitivity results were driven by one of the parameters only, these results are provided in Appendix D. In sections 3.2.4.1 and 3.2.4.2 the results referred to are the ICER (rather than net benefit).

3.2.4.1 Relative risk and cost of intervention

Figure 3.10 displays the two-way sensitivity analysis where both the cost of medicine reconciliation and the relative risk of medicine reconciliation are varied simultaneously. It shows that where the cost of the intervention and relative risk are high, medicine reconciliation is not cost-effective at a £20,000 per QALY threshold. As the intervention becomes more effective and cheaper the ICER reduces.

3.2.4.2 QALY loss and proportion of severe pADEs

The two-way sensitivity analysis, whereby the proportion of severe pADEs and the QALY loss associated with PADEs were varied simultaneously, is displayed in Figure 3.11. Where the proportion of pADE that are severe and the QALY loss associated with these severe pADE are low, the cost per QALY of medicine reconciliation increases. This occurs because where there exists a low baseline number of severe pADEs that are have low relative severity (i.e. their impact on quality of life is small); there is less scope for medicine reconciliation to provide improvement. As the proportion of severe pADE increases and the QALY loss associated with those pADEs increases, there exists a greater capacity for improvement following medicine reconciliation.

Figure 3.10: Two-way sensitivity analysis – cost and relative risk of medication error with medicine reconciliation

Cost of intervention	Relative risk of intervention								
	0.52	0.6	0.65	0.7	0.75	0.8	0.85	0.9	0.99
£36	£3,173	£4,376	£5,407	£6,781	£8,706	£11,592	£16,403	£26,025	£285,819
£40	£3,841	£5,178	£6,323	£7,850	£9,989	£13,196	£18,542	£29,233	£317,892
£50	£5,512	£7,182	£8,614	£10,523	£13,196	£17,205	£23,887	£37,251	£398,076
£60	£7,182	£9,187	£10,905	£13,196	£16,403	£21,214	£29,233	£45,269	£478,259
£70	£8,853	£11,191	£13,196	£15,869	£19,611	£25,224	£34,578	£53,288	£558,442
£80	£10,523	£13,196	£15,487	£18,542	£22,818	£29,233	£39,924	£61,306	£638,625
£90	£12,194	£15,201	£17,778	£21,214	£26,025	£33,242	£45,269	£69,324	£718,809
£100	£13,864	£17,205	£20,069	£23,887	£29,233	£37,251	£50,615	£77,343	£798,992
£110	£15,535	£19,210	£22,360	£26,560	£32,440	£41,260	£55,960	£85,361	£879,175
£120	£17,205	£21,214	£24,651	£29,233	£35,647	£45,269	£61,306	£93,379	£959,358
£124	£17,873	£22,016	£25,567	£30,302	£36,930	£46,873	£63,444	£96,587	£991,432

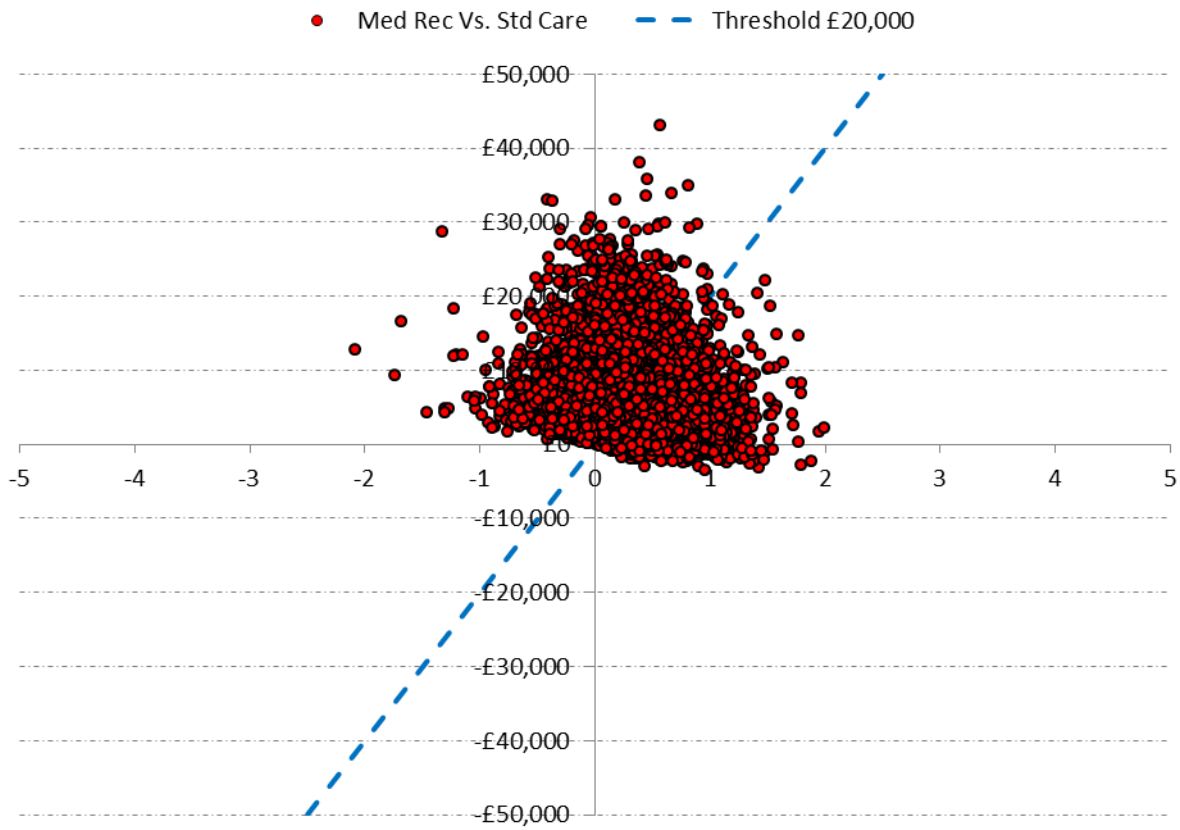
Figure 3.11: Two-way sensitivity analysis – QALY loss and proportion of severe pADE

QALY loss of severe pADE	Proportion of severe pADE										
	0.00	0.04	0.08	0.12	0.16	0.20	0.24	0.28	0.32	0.36	0.40
1.0000	£143,341	£82,596	£57,674	£44,103	£35,566	£29,700	£25,422	£22,163	£19,598	£17,527	£15,820
1.3000	£143,341	£73,389	£49,004	£36,601	£29,091	£24,055	£20,443	£17,727	£15,609	£13,912	£12,522
1.6000	£143,341	£66,029	£42,600	£31,281	£24,610	£20,213	£17,095	£14,770	£12,969	£11,534	£10,362
1.9000	£143,341	£60,011	£37,677	£27,311	£21,326	£17,429	£14,690	£12,659	£11,093	£9,850	£8,837
2.2000	£143,341	£54,998	£33,773	£24,235	£18,815	£15,319	£12,878	£11,076	£9,692	£8,595	£7,704
2.5000	£143,341	£50,758	£30,603	£21,782	£16,833	£13,665	£11,463	£9,845	£8,604	£7,623	£6,828
2.8000	£143,341	£47,125	£27,976	£19,780	£15,228	£12,333	£10,329	£8,860	£7,736	£6,849	£6,131
3.1000	£143,341	£43,977	£25,765	£18,115	£13,903	£11,238	£9,399	£8,054	£7,027	£6,218	£5,563
3.4000	£143,341	£41,224	£23,878	£16,708	£12,791	£10,321	£8,623	£7,383	£6,437	£5,693	£5,092
3.7000	£143,341	£38,794	£22,248	£15,504	£11,843	£9,543	£7,965	£6,815	£5,939	£5,250	£4,694
4.4100	£143,341	£34,047	£19,155	£13,246	£10,075	£8,098	£6,747	£5,765	£5,019	£4,433	£3,961

3.3 PROBABILISTIC SENSITIVITY ANALYSIS

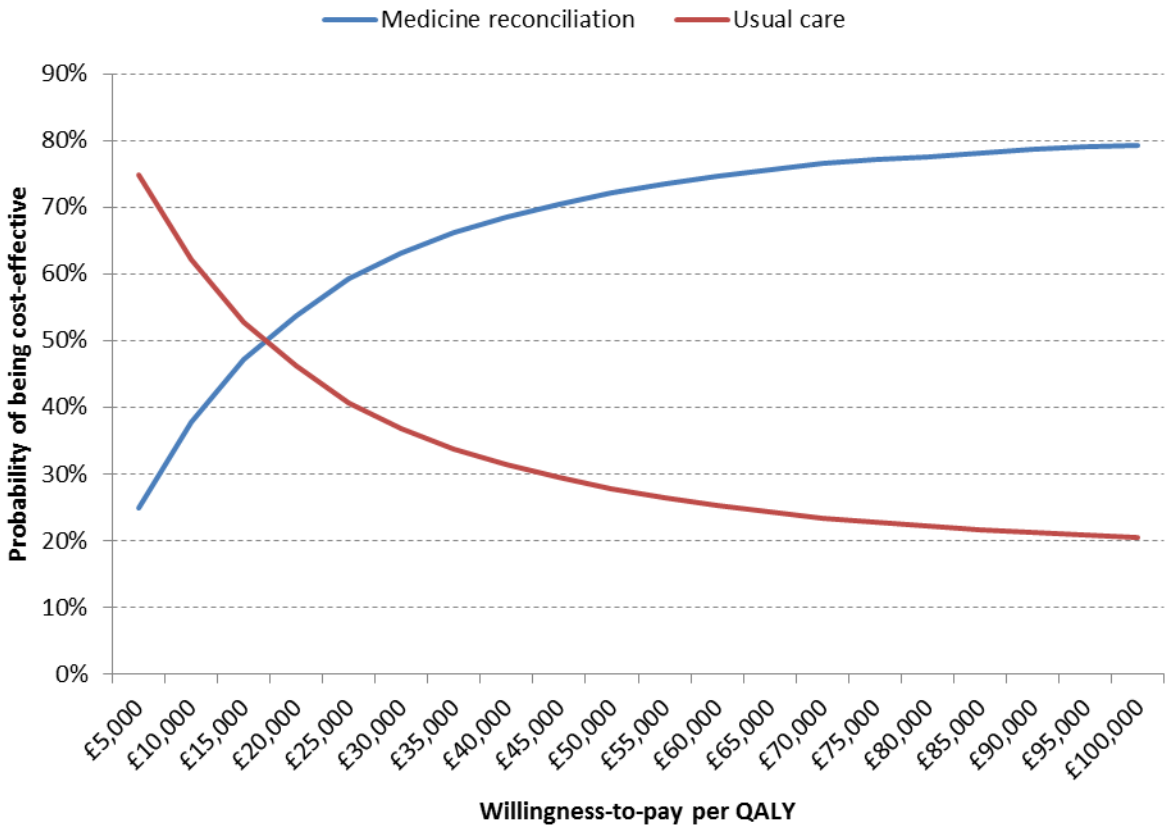
With a threshold of £20,000 per QALY, medicine reconciliation was cost-effective versus usual care in 53.7% of iterations. This is displayed in Figure 3.12, where the blue dotted line represents the threshold for cost-effectiveness and points to the right of this line are considered cost-effective. At a threshold of £30,000 medicine reconciliation is cost-effective versus usual care in 63.15% of iterations. Given the lack of data available to inform uncertainty around many of the point estimates, uniform distribution was assumed within ranges taken from the literature and as such the results of the probabilistic sensitivity analysis should be treated with caution.

Figure 3.12: Probabilistic sensitivity analysis (£20,000 threshold)



A cost-effectiveness acceptability curve (CEAC) can be generated, and is displayed in Figure 3.13. The CEAC shows the likelihood that medicine reconciliation is cost-effective versus usual care as the cost paid per QALY gained is varied. As the cost paid increases the likelihood that medicine reconciliation is cost-effective also increases. Figure 3.13 shows that medicine reconciliation is more likely to be cost-effective than not, versus usual care at a WTP threshold of around £17,000

Figure 3.13: Cost-effectiveness acceptability curve



Section 4: Discussion and Conclusion

4.1 DISCUSSION

The base-case results of the model suggest that medicine reconciliation throughout the hospital visit is cost-effective compared with usual care at a threshold of £20,000 per QALY. Probabilistic sensitivity analysis suggests that there is a 53.7% probability that medicines reconciliation throughout a hospital visit will be cost-effective at a threshold of £20,000 per QALY. This reflects the impact of the uncertainty of key parameters on cost-effectiveness, notably the risk reduction of pADE with medicine reconciliation and the cost of this intervention.

4.2 LIMITATIONS

The model findings are limited by the availability of evidence on key parameters. These are discussed in more detail in subsequent sections.

4.2.1 Effectiveness of medicine reconciliation

The model was based upon RCT data identified during the clinical evidence review for this guideline. Although four RCTs were included within the clinical evidence, only one of these was appropriate for use to populate the model because the risk reduction of medication errors associated with medicine reconciliation compared to usual care could not be calculated from the remaining three studies. The rationale for this is provided in Section 2.2. Medicine reconciliation within the included RCT was a package of interventions that were undertaken at several points during a hospital admission and by different healthcare professionals. No RCT data suitable for use in the model was identified for medicine reconciliation as a one-off e.g. at admission or discharge, or in any other settings. The model, therefore, was limited to considering a medicine reconciliation intervention compared with usual care as set out in the RCT by Schnipper *et al.* (2009).

The RCT used within the model was deemed to be of low quality during the clinical evidence review. Further, it was set in two US hospitals and as such may not be of full relevance to the current NHS. This evidence, however, was the best available evidence identified that could be used within the model.

Schnipper *et al.* (2009) reported the relative risk of medication error with medicine reconciliation versus usual care to be 0.72, suggesting that reconciling medicines has a substantial impact on reducing medication errors. This shows that undertaking medicine reconciliation throughout a hospital stay resulted in 72% reduction in the risk of the medication errors that occurred without medicine reconciliation. A wide 95% confidence interval was reported (0.52-0.99) and when sensitivity analysis was carried out in the model

using this range, relative risk was to be a key driver of the model. Threshold analysis suggested that in order for the intervention to be considered cost-effective at a £20,000 per QALY threshold the relative risk with the intervention must be 0.81, or less and at a £30,000 per QALY threshold must be 0.86 or less. Future research may be merited to provide more certainty around the effectiveness of medicine reconciliation, particularly in a UK NHS setting or in settings other than an acute setting. If further research does become available, Figure 3.10 may be utilised to determine the likely updated ICER (based on new relative risk and the likely cost of the intervention).

4.2.2 Baseline risks

Other input parameters within the model were the baseline risk of error, probability of error detection and probability of harm from undetected errors, all of which were broken down into errors of omission, errors of commission and errors due to known allergies. The type of pADE were split into severe (fatal/life threatening), serious or significant. With the exception of baseline error rates, these parameters were drawn from non-UK studies, as such the relevance to the UK NHS may be limited. No further UK based evidence was identified; however, studies conducted suggest that variations exist in the magnitude and type of prescribing errors within the NHS (Franklin *et al.*, 2011). As such, it is likely that differences exist between the US and the UK; although estimating the direction and magnitude of these differences is difficult and in doing so may introduce further uncertainty into the model.

Univariate sensitivity analysis highlighted the probability of severe pADE as a key driver of the model. Within the literature, no confidence measures were provided alongside the point estimates, and as such, the certainty of the values used within the base case of this model are unknown. In order to overcome this, data from other studies measuring the severity of pADEs were inputted into the model. Use of data from Bates *et al*. (1995a) and (1995b) generated a lower ICER than that of the base case using data by Hug *et al.* (2010). It is important to note that all three of these studies were set in the US and no data from the UK were identified.

4.2.3 Resource use and costs

The resource use required to deliver medicine reconciliation as delivered in the RCT on which this economic model is based had to be estimated using other sources as no information on resource use was provided by Schnipper *et al*. Therefore, uncertainty exists around the cost of the intervention. Table 3.2 provided various scenarios for consideration by the GDG of the upper limit of resources used during medicine reconciliation in order for it to remain a cost-effective option versus usual care at a threshold of £20,000 per QALY. Table 3.3 shows that at a £20,000 per QALY threshold the intervention must cost no more than £79.75 per person in order to be considered cost-effective and at a £30,0000 per QALY threshold no more than £114.67 per person.

The cost of pADEs were taken from Karnon *et al*., (2009) and inflated to 2012/12 costs. It was evident from the univariate sensitivity analysis that varying these costs had almost no

impact on the results of the model. This occurred because the proportion of prescription orders actually resulting in pADEs was very small.

4.2.4 Utility and QALYs following a pADE

The key data gap in the analysis undertaken by Karnon *et al.* (2009) was the lack of quality of life evidence. Our utility review identified no relevant studies having been published since the previous analysis. As such, the QALY loss associated with pADEs was taken from estimations using assumptions made by Karnon *et al*. Future research into the impact on quality of life following pADEs using generic tool such as the EQ-5D is merited, however, it is acknowledged that deriving QALY loss for patients experiencing adverse drug events from any medication is difficult.

Sensitivity analysis was conducted around wide ranges of QALY loss in order to assess the importance of the uncertainty around these parameters. The results of this suggest that varying the QALY loss associated with serious and significant pADEs has little impact on the results of the model, however, the QALY loss associated with fatal or life-threatening pADEs is more of a key driver. The GDG attempted to consider whether it is reasonable to assume that the QALY loss occurring from a severe pADE (fatal or life threatening) is greater than 1.6 QALYs, but found it difficult to quantify QALY, or indeed utility, loss from severe pADE in any hospitalised patient given the variation in health states of hospitalised patients.

4.2.5 Probabilistic sensitivity analysis

During probabilistic sensitivity analysis a range for each input parameter was considered rather than using one fixed value for each input. The model was run 10,000 times, each iteration using a different set of values for the inputs. Ideally, information would be available around the uncertainty surrounding mean input parameters, for example, through a measure of dispersion such as a standard deviation or standard error. Many of the inputs used within the model were provided as a range and therefore the mid-point of this range was used as a point estimate in the base case. A uniform distribution of this range was assumed, meaning that each value within the range is equally likely. Should information on the uncertainty that surrounds all the point estimates in the model have been available (as was the case for the RR associated with medicine reconciliation from Schnipper *et al*., 2009) the probabilistic sensitivity analysis would have been more meaningful. The true uncertainty around the results of the model may be higher or lower than currently determined by the probabilistic sensitivity analysis depending on actual uncertainty around parameter inputs.

4.3 COMPARISONS WITH PUBLISHED STUDIES

The only published study meeting the inclusion criteria for this area of the clinical guideline was that by Karnon *et al*. (2009) on which this model is based. This study utilised clinical data which were largely from observational studies and that were excluded as part of the clinical review. The analysis was judged to have potentially serious limitations as part of the

economic review. A comparison of the findings from that study and that reported here using RCT data is therefore not especially meaningful.

Karnon *et al.* (2009) did find medicines reconciliation in various forms to be cost effective as this study also found. The cost effectiveness ratios were more favourable then this study found which in part is due to the more costly intervention analysed in this study. This is unambiguous and the fact the studies were observational as opposed to RCT in combination with the lower derived costs suggests that the difference in included study types had little effect on the cost differentials. The nature of the intervention in Schnipper *et al.* (2009) is likely to be more resource intensive and costly than those considered by Karnon *et al.* (2009).

The cost effectiveness ratios are also more favourable in Karnon *et al.* (2009) because of the greater risk reduction for the interventions in the observational studies they include. How much of this difference in risk reduction is real and how much due to study design biasing a positive result for the intervention cannot be deciphered.

Whilst it is encouraging that the findings from Karnon *et al.* (2009) on the cost-effectiveness of medicines reconciliation are similar to those reported here, comparing the findings closely to those here to inform the best method of medicines reconciliation is not helpful for decision makers as the different evidence sources could mislead to poor conclusions.

4.4 IMPLICATIONS FOR FURTHER RESEARCH

Due to the paucity of published evidence discussed above, the economic model presented in this report was necessarily based on a number of assumptions. Future research may be conducted to inform these assumptions and build upon the existing evidence base, particularly in the following areas:

- Collection of quality of life data using EQ-5D on pADEs from medication errors;
- UK based randomised control trials comparing medicine reconciliation (in various forms) with usual care which report the relative risk of prescribing errors between interventions;
- Collection of data around resource use with and without medicines reconciliation;
- Analysis of the rate of medication errors, the likelihood of detection of these errors and the probability of harm from these errors;
- Analysis of the degree of severity of pADE and the proportion in which different levels of severity occur.

4.5 CONCLUSION (EVIDENCE STATEMENT)

Economic modelling suggests that medicine reconciliation throughout a hospital stay appears to be a cost-effective use of NHS resources; however considerable uncertainty

exists around this finding. There is no evidence to suggest that medicines reconciliation in settings outside of the acute sector is or is not cost-effective.

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APPENDIX A

Search Strategy for Utility Review

A.1: Source: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Interface / URL: OvidSP
Search date: 09/06/14
Retrieved records: 1276
Search strategy:

1 exp Hospitals/ 203530
2 exp Hospitalization/ 158835
3 exp Hospital Units/ 77913
4 exp Hospital Departments/ 145709
5 Hospital Shared Services/ 2134
6 Medication Systems, Hospital/ 3140
7 personnel, hospital/ or dental staff, hospital/ or exp medical staff, hospital/ or nursing staff, hospital/ 69929
8 Inpatients/ 12896
9 (hospital$ or inpatient$ or "in-patient").ti,ab,kf. 905663
10 Secondary Care/ or Tertiary Healthcare/ 301
11 ((acute or secondary or tertiary) adj2 (care or healthcare or setting$)).ti,ab,kf. 56305
12 (admission$ or admitted).ti,ab,kf. 236574
13 (ward or wards).ti,ab,kf. 40415
14 or/1-13 1299841
15 (to or po).fs. 382882
16 exp "Drug-Related Side Effects and Adverse Reactions"/ 88137
17 exp drug toxicity/ 88137
18 toxicity.ti,ab,kf. 256685
19 Drug Monitoring/ 14340
20 (ADE or ADEs or ADR or ADRs or AME or AMEs or AMR or AMRs).ti,ab,kf. 15302
21 or/15-20 653299
22 (ae or co).fs. 2772117
23 exp Product Surveillance, Postmarketing/ 11111
24 complication$.ti,ab,kf. 652297
25 ((adverse or undesirable or harm$ or serious or critical or safety) adj3 (effect$1 or incident$1 or reaction$1 or event$1 or outcome$1)).ti,ab,kf. 292047
26 (side effect$1 or harms).ti,ab,kf. 186605
27 (clinical incident$1 or incident report$).ti,ab,kf. 1445
28 or/22-27 3368770
29 (aa or ad or ag or ai or ct or de or dt or pd or pk or tu).fs. 5524682
30 exp Drug Therapy/ 1077180
31 exp Pharmaceutical Preparations/ 630685
32 exp Drug Interactions/140487
33 exp Medication Systems/ 4152
34 exp Drug Prescriptions/ 24080
35 exp Pharmaceutical Services/ 49114

36 (medication$ or medicine$ or drug$1 or chemotherap$ or chemo-therap$ or prescription$ or prescrib$ or pharmac$ or dose$1 or dosage$1 or dosing or agent$1 or dispens$).ti,ab,kf. 3393329
37 or/29-36 7209507
38 28 and 37 1427282
39 21 or 38 1926885
40 Quality-Adjusted Life Years/ 6976
41 (quality adjusted or adjusted life year$).ti,ab,kf. 8183
42 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. 5384
43 disability adjusted life.ti,ab,kf. 1323
44 daly$1.ti,ab,kf. 1280
45 (utility or utilities or disutility or disutilities).ti,ab,kf. 120558
46 (health state$1 or health status or illness state$1 or illness status).ti,ab,kf. 40948
47 ((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kf. 373
48 (multiattribute$ or multi attribute$).ti,ab,kf. 507
49 health$1 year$1 equivalent$1.ti,ab,kf. 40
50 (hye or hyes).ti,ab,kf. 55
51 (hui or hui1 or hui2 or hui3).ti,ab,kf. 933
52 (euro qual or euro qol or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kf. 4240
53 (short form$ or shortform$).ti,ab,kf. 18061
54 (sf36$ or sf 36$ or sf thirtysix$ or sf thirty six$).ti,ab,kf. 13934
55 (sf6$ or sf 6$ or sf six$ or sfsix$ or sf8 or sf 8 or sf eight or sfeight).ti,ab,kf. 2263
56 (sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf. 2316
57 (sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kf. 18
58 (sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kf. 300
59 standard gamble$.ti,ab,kf. 677
60 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. 1210
61 or/40-60 194943
62 14 and 39 and 61 2267
63 exp Medication Errors/ 11088
64 ((medication$ or medicine$ or drug$1 or chemotherap$ or chemo-therap$ or prescription$ or prescrib$ or pharmac$ or dose$1 or dosage$1 or dosing or agent$1 or dispens$) adj3 (error$ or mistake$ or incident$1)).ti,ab,kf. 7496
65 or/63-64 14988
66 65 and 61 105
67 62 or 66 2350
68 (letter or editorial or comment or news).pt. 1487315
69 exp animals/ not humans/ 3947170
70 67 not (68 or 69) 2329
71 (2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$).ed,dc,dp,ep,vd,yr. 7315095
72 70 and 71 1410
73 limit 72 to english language 1337
74 remove duplicates from 73 1276

Key to Ovid symbols and commands

.ti,ab,kf.	Restricts search to title, abstract and keyword headings fields
/	Restricts search to Medical Subject Headings (MeSH)
exp	Indicates an exploded Medical Subject Heading (MeSH)
.fs.	Floating subheading
$	Truncation symbol
.pt.	Restricts search to publication type field
?	Wildcard symbol
adj3	Words must appear with 3 words of each other
or/1-9	Combine sets 1 to 9 using OR

A.2: Source: NHS Economic Evaluation Database (NHS EED) - Issue 2 of 4, April 2014

Interface / URL: Cochrane Library/Wiley Interscience
Search date: 09/06/14
Retrieved records: 900
Search strategy:

#1 [mh Hospitals] 2955
#2 [mh Hospitalization] 12168
#3 [mh "Hospital Units"] 3106
#4 [mh "Hospital Departments"] 2988
#5 [mh ^"Hospital Shared Services"] 2
#6 [mh ^"Medication Systems, Hospital"] 48
#7 [mh ^"personnel, hospital"] or [mh ^"dental staff, hospital"] or [mh "medical staff, hospital"] or [mh ^"nursing staff, hospital"] 772
#8 [mh ^Inpatients] 666
#9 (hospital* or inpatient* or "in-patient") 173173
#10 [mh ^"Secondary Care"] or [mh ^"Tertiary Healthcare"] 12
#11 ((acute or secondary or tertiary) near/2 (care or healthcare or setting*)) 9165
#12 (admission* or admitted) 20079
#13 (ward or wards) 6643
#14 {or #1-#13} 184679
#15 Any MeSH descriptor with qualifier(s): [Poisoning - PO, Toxicity - TO] 1822
#16 [mh "Drug-Related Side Effects and Adverse Reactions"] 2326
#17 [mh "drug toxicity"] 2326
#18 toxicity 18482
#19 [mh ^"Drug Monitoring"] 1095
#20 (ADE or ADEs or ADR or ADRs or AME or AMEs or AMR or AMRs) 1282
#21 {or #15-#20} 23020
#22 Any MeSH descriptor with qualifier(s): [Adverse effects - AE, Complications - CO] 136389
#23 [mh "Product Surveillance, Postmarketing"] 220
#24 complication* 98233
#25 ((adverse or undesirable or harm* or serious or critical or safety) near/3 (effect* or affect* or incident* or reaction* or event* or outcome*)) 164794

#26 (side next effect* or harms) 60641
#27 (clinical next incident* or incident next report*) 70
#28 {or #22-#27} 246570
#29 Any MeSH descriptor with qualifier(s): [Administration & dosage - AD, Agonists - AG, Analogs & derivatives - AA, Antagonists & inhibitors - AI, Contraindications - CT, Drug effects - DE, Drug therapy - DT, Pharmacokinetics - PK, Pharmacology - PD, Therapeutic use - TU] 303684
#30 [mh "Drug Therapy"] 116912
#31 [mh "Pharmaceutical Preparations"] 56217
#32 [mh "Drug Interactions"] 7077
#33 [mh "Medication Systems"] 99
#34 [mh "Drug Prescriptions"] 610
#35 [mh "Pharmaceutical Services"] 1282
#36 (medication* or medicine* or drug* or chemotherap* or chemo-therap* or prescription* or prescrib* or pharmac* or dose* or dosage* or dosing or agent* or dispens*) 509874
#37 {or #29-#36} 522124
#38 #28 and #37 204664
#39 #21 or #38 212349
#40 [mh ^"Quality-Adjusted Life Years"] 3609
#41 ("quality adjusted" or adjusted next life next year*) 6242
#42 (qaly* or qald* or qale* or qtime*) 3853
#43 (disability next adjusted next life) 300
#44 daly* 868
#45 (utility or utilities or disutility or disutilities) 10487
#46 (health next state* or "health status" or illness next state* or "illness status") 8856
#47 ((index near/3 wellbeing) or (quality near/3 wellbeing) or qwb) 133
#48 (multiattribute* or multi next attribute*) 60
#49 (health* next year* next equivalent*) 5
#50 (hye or hyes) 44
#51 (hui or hui1 or hui2 or hui3) 1107
#52 ("euro qual" or "euro qol" or "euro qual5d" or "euro qol5d" or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d) 2152
#53 (short next form* or shortform*) 4270
#54 (sf36* or sf next 36* or sf next thirtysix* or sf next thirty next six*) 4197
#55 (sf6* or sf next 6* or sf next six* or sfsix* or sf8 or sf next 8 or sf next eight or sfeight) 6092
#56 (sf12 or "sf 12" or "sf twelve" or sftwelve) 625
#57 (sf16 or "sf 16" or "sf sixteen" or sfsixteen) 6
#58 (sf20 or "sf 20" or "sf twenty" or sftwenty) 60
#59 (standard next gamble*) 294
#60 (time next trade next off* or time next tradeoff* or tto or timetradeoff*) 513
#61 {or #40-#60} 28970
#62 #14 and #39 and #61 5795
#63 [mh "Medication Errors"] 263

#64 ((medication* or medicine* or drug* or chemotherap* or chemo-therap* or prescription* or prescrib* or pharmac* or dose* or dosage* or dosing or agent* or dispens*) near/3 (error* or mistake* or incident*)) 674
#65 #63 or #64 713
#66 #65 and #61 65
#67 #62 or #66 5818
#68 #67 in Economic Evaluations 900 [Limit applied: Publication Date between 2007 and 2014]

A.3: Source: Health Technology Assessment Database (HTA) - Issue 2 of 4 Apr 2014

Interface / URL: Cochrane Library/Wiley Interscience
Search date: 09/06/14
Retrieved records: 55
Search strategy:

#1 [mh Hospitals] 2955
#2 [mh Hospitalization] 12168
#3 [mh "Hospital Units"] 3106
#4 [mh "Hospital Departments"] 2988
#5 [mh ^"Hospital Shared Services"] 2
#6 [mh ^"Medication Systems, Hospital"] 48
#7 [mh ^"personnel, hospital"] or [mh ^"dental staff, hospital"] or [mh "medical staff, hospital"] or [mh ^"nursing staff, hospital"] 772
#8 [mh ^Inpatients] 666
#9 (hospital* or inpatient* or "in-patient") 173173
#10 [mh ^"Secondary Care"] or [mh ^"Tertiary Healthcare"] 12
#11 ((acute or secondary or tertiary) near/2 (care or healthcare or setting*)) 9165
#12 (admission* or admitted) 20079
#13 (ward or wards) 6643
#14 {or #1-#13} 184679
#15 Any MeSH descriptor with qualifier(s): [Poisoning - PO, Toxicity - TO] 1822
#16 [mh "Drug-Related Side Effects and Adverse Reactions"] 2326
#17 [mh "drug toxicity"] 2326
#18 toxicity 18482
#19 [mh ^"Drug Monitoring"] 1095
#20 (ADE or ADEs or ADR or ADRs or AME or AMEs or AMR or AMRs) 1282
#21 {or #15-#20} 23020
#22 Any MeSH descriptor with qualifier(s): [Adverse effects - AE, Complications - CO] 136389
#23 [mh "Product Surveillance, Postmarketing"] 220
#24 complication* 98233
#25 ((adverse or undesirable or harm* or serious or critical or safety) near/3 (effect* or incident* or reaction* or event* or outcome*)) 164689

#26 (side next effect* or harms) 60641
#27 (clinical next incident* or incident next report*) 70
#28 {or #22-#27} 246486
#29 Any MeSH descriptor with qualifier(s): [Administration & dosage - AD, Agonists - AG, Analogs & derivatives - AA, Antagonists & inhibitors - AI, Contraindications - CT, Drug effects - DE, Drug therapy - DT, Pharmacokinetics - PK, Pharmacology - PD, Therapeutic use - TU] 303684
#30 [mh "Drug Therapy"] 116912
#31 [mh "Pharmaceutical Preparations"] 56217
#32 [mh "Drug Interactions"] 7077
#33 [mh "Medication Systems"] 99
#34 [mh "Drug Prescriptions"] 610
#35 [mh "Pharmaceutical Services"] 1282
#36 (medication* or medicine* or drug* or chemotherap* or chemo-therap* or prescription* or prescrib* or pharmac* or dose* or dosage* or dosing or agent* or dispens*) 509874
#37 {or #29-#36} 522124
#38 #28 and #37 204611
#39 #21 or #38 212297
#40 [mh ^"Quality-Adjusted Life Years"] 3609
#41 ("quality adjusted" or adjusted next life next year*) 6242
#42 (qaly* or qald* or qale* or qtime*) 3853
#43 (disability next adjusted next life) 300
#44 daly* 868
#45 (utility or utilities or disutility or disutilities) 10487
#46 (health next state* or "health status" or illness next state* or "illness status") 8856
#47 ((index near/3 wellbeing) or (quality near/3 wellbeing) or qwb) 133
#48 (multiattribute* or multi next attribute*) 60
#49 (health* next year* next equivalent*) 5
#50 (hye or hyes) 44
#51 (hui or hui1 or hui2 or hui3) 1107
#52 ("euro qual" or "euro qol" or "euro qual5d" or "euro qol5d" or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d) 2152
#53 (short next form* or shortform*) 4270
#54 (sf36* or sf next 36* or sf next thirtysix* or sf next thirty next six*) 4197
#55 (sf6* or sf next 6* or sf next six* or sfsix* or sf8 or sf next 8 or sf next eight or sfeight) 6092
#56 (sf12 or "sf 12" or "sf twelve" or sftwelve) 625
#57 (sf16 or "sf 16" or "sf sixteen" or sfsixteen) 6
#58 (sf20 or "sf 20" or "sf twenty" or sftwenty) 60
#59 (standard next gamble*) 294
#60 (time next trade next off* or time next tradeoff* or tto or timetradeoff*) 513
#61 {or #40-#60} 28970
#62 #14 and #39 and #61 5793
#63 [mh "Medication Errors"] 263

#64 ((medication* or medicine* or drug* or chemotherap* or chemo-therap* or prescription* or prescrib* or pharmac* or dose* or dosage* or dosing or agent* or dispens*) near/3 (error* or mistake* or incident*)) 674
#65 #63 or #64 713
#66 #65 and #61 65
#67 #62 or #66 5816
#68 #67 in Economic Evaluations 900
#69 #14 and #39 72711
#70 #69 or #65 in Technology Assessments 122

[Note: Date limit functionality not working in Cochrane Library. Unable to apply date limits to HTA results, has no impact. Imported all 122 records into an Endnote library and deleted results with publication date before 2007 by hand. 67 pre-2007 results deleted, 55 results retrieved for import into main results Endnote Library]

A.4: Source: Embase 1974 to 2014 June 06

Interface / URL: OvidSP
Search date: 09/06/14
Retrieved records: 2029
Search strategy:

1 exp *hospital/ 220064
2 *hospitalization/ 23544
3 *hospital service/ 7563
4 *hospital organization/ 6449
5 exp *hospital personnel/ 29373
6 *nursing staff/ 39625
7 exp *hospital patient/ 12388
8 (hospital$ or inpatient$ or "in-patient").ti,ab,kw. 1219663
9 exp *secondary health care/ or exp *tertiary health care/ 3713
10 ((acute or secondary or tertiary) adj2 (care or healthcare or setting$)).ti,ab,kw. 75912
11 *hospital admission/ 11698
12 (admission$ or admitted).ti,ab,kw. 343338
13 (ward or wards).ti,ab,kw. 55890
14 or/1-13 1563542
15 ae.fs. 1089234
16 exp *adverse drug reaction/ 156856
17 exp *"drug toxicity and intoxication"/ 60354
18 toxicity.ti,ab,kw. 337223
19 *drug monitoring/ 17246
20 *drug safety/ 12619
21 (ADE or ADEs or ADR or ADRs or AME or AMEs or AMR or AMRs).ti,ab,kw. 21703
22 or/15-21 1556916
23 si.fs. 697448
24 exp *postmarketing surveillance/ 10330
25 *complication/ 1661
26 complication$.ti,ab,kw. 817678
27 ((adverse or undesirable or harm$ or serious or critical or safety) adj3 (effect$1 or incident$1 or reaction$1 or event$1 or outcome$1)).ti,ab,kw. 411363
28 (side effect$1 or harms).ti,ab,kw. 247835
29 (clinical incident$1 or incident report$).ti,ab,kw. 2004
30 or/23-29 1870347
31 (ad or ar or bd or br or bu or ca or cb or ce or ci or cj or cl or cm or cr or cv or dl or do or dr or dt or du or ei or ia or ic or ig or ih or il or im or io or ip or it or iv or li or ly or na or oc or os or pa or pl or po or pr or rb or rc or rp or sb or sc or sp or td or tl or tp or tr or tu or ty or ur or ut or va or ve or vi).fs. 3814682
32 exp *drug therapy/ 588631
33 exp *drug/ 96514
34 exp *pharmacodynamics/ 640499

35 exp *"drug use"/ 37792
36 *hospital pharmacy/ 7397
37 *pharmacy/ 30392
38 (medication$ or medicine$ or drug$1 or chemotherap$ or chemo-therap$ or prescription$ or prescrib$ or pharmac$ or dose$1 or dosage$1 or dosing or agent$1 or dispens$).ti,ab,kw. 4345149
39 or/31-38 7098955
40 30 and 39 1173260
41 22 or 40 1977579
42 *quality adjusted life year/ 774
43 (quality adjusted or adjusted life year$).ti,ab,kw. 10836
44 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. 8833
45 disability adjusted life.ti,ab,kw. 1557
46 daly$1.ti,ab,kw. 1663
47 (utility or utilities or disutility or disutilities).ti,ab,kw. 153709
48 *health status/ 24301
49 (health state$1 or health status or illness state$1 or illness status).ti,ab,kw. 50796
50 ((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).ti,ab,kw. 543
51 (multiattribute$ or multi attribute$).ti,ab,kw. 644
52 health$1 year$1 equivalent$1.ti,ab,kw. 41
53 (hye or hyes).ti,ab,kw.98
54 (hui or hui1 or hui2 or hui3).ti,ab,kw. 1292
55 (euro qual or euro qol or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).ti,ab,kw. 6979
56 *short form 12/ or *short form 20/ or *short form 36/ or *short form 8/ or *short form 6D/ 525
57 (short form$ or shortform$).ti,ab,kw. 22361
58 (sf36$ or sf 36$ or sf thirtysix$ or sf thirty six$).ti,ab,kw. 20705
59 (sf6$ or sf 6$ or sf six$ or sfsix$ or sf8 or sf 8 or sf eight or sfeight).ti,ab,kw. 2822
60 (sf16 or sf 16 or sf sixteen or sfsixteen).ti,ab,kw. 31
61 (sf20 or sf 20 or sf twenty or sftwenty).ti,ab,kw. 280
62 standard gamble$.ti,ab,kw. 794
63 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw. 1574
64 or/42-63 260871
65 14 and 41 and 64 2968
66 *medication error/ 6287
67 ((medication$ or medicine$ or drug$1 or chemotherap$ or chemo-therap$ or prescription$ or prescrib$ or pharmac$ or dose$1 or dosage$1 or dosing or agent$1 or dispens$) adj3 (error$ or mistake$ or incident$1)).ti,ab,kw. 11332
68 or/66-67 14351
69 68 and 64 112
70 65 or 69 3056
71 (editorial or letter).pt. 1295101
72 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ 4945404

73 70 not (71 or 72) 3040
74 (2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$).em,dp,yr,dd. 10037338
75 73 and 74 2170
76 limit 75 to english language 2061
77 remove duplicates from 76 2029

A.5: Source: Econlit 1886 to May 2014

Interface / URL: OvidSP
Search date: 09/08/14
Retrieved records: 9
Search strategy:

1 (hospital$ or inpatient$ or "in-patient").af. 6375
2 ((acute or secondary or tertiary) adj2 (care or healthcare or setting$)).af. 209
3 (admission$ or admitted).af. 1614
4 (ward or wards).af. 470
5 or/1-4 8089
6 toxicity.af. 109
7 (ADE or ADEs or ADR or ADRs or AME or AMEs or AMR or AMRs).af. 1104
8 or/6-7 1212
9 complication$.af. 718
10 ((adverse or undesirable or harm$ or serious or critical or safety) adj3 (effect$1 or incident$1 or reaction$1 or event$1 or outcome$1)).af. 3728
11 (side effect$1 or harms).af. 1221
12 (clinical incident$1 or incident report$).af. 5
13 or/9-12 5538
14 (medication$ or medicine$ or drug$1 or chemotherap$ or chemo-therap$ or prescription$ or prescrib$ or pharmac$ or dose$1 or dosage$1 or dosing or agent$1 or dispens$).af. 46417
15 13 and 14 510
16 8 or 15 1715
17 (quality adjusted or adjusted life year$).af. 534
18 (qaly$ or qald$ or qale$ or qtime$).af. 327
19 disability adjusted life.af. 56
20 daly$1.af. 146
21 (utility or utilities or disutility or disutilities).af. 37828
22 (health state$1 or health status or illness state$1 or illness status).af. 1750
23 ((index adj3 wellbeing) or (quality adj3 wellbeing) or qwb).af. 52
24 (multiattribute$ or multi attribute$).af. 445
25 health$1 year$1 equivalent$1.af. 15
26 (hye or hyes).af. 21
27 (hui or hui1 or hui2 or hui3).af. 91
28 (euro qual or euro qol or euro qual5d or euro qol5d or eq-5d or eq5-d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d).af. 93
29 (short form$ or shortform$).af. 45
30 (sf36$ or sf 36$ or sf thirtysix$ or sf thirty six$).af. 35
31 (sf6$ or sf 6$ or sf six$ or sfsix$ or sf8 or sf 8 or sf eight or sfeight).af. 37
32 (sf12 or sf 12 or sf twelve or sftwelve).af. 9
33 (sf16 or sf 16 or sf sixteen or sfsixteen).af. 0
34 (sf20 or sf 20 or sf twenty or sftwenty).af. 0
35 standard gamble$.af. 71
36 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).af. 132

37 or/17-36 40480
38 5 and 16 and 37 8
39 ((medication$ or medicine$ or drug$1 or chemotherap$ or chemo-therap$ or prescription$ or prescrib$ or pharmac$ or dose$1 or dosage$1 or dosing or agent$1 or dispens$) adj3 (error$ or mistake$ or incident$1)).af. 84
40 39 and 37 3
41 38 or 40 11
42 (2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$).up,yr,dp. 559229
43 41 and 42 9
44 limit 43 to english 9

A.6: Source: HEED: Health Economic Evaluations Database

Interface / URL: EBSCOHOST
Search date: 09/06/14
Retrieved records: 144
Search strategy:

S42 S38 OR S40 Limiters - Published Date: 20070101-20141231; Language: English 144
S41 S38 OR S40 300
S40 S37 AND S39 5
S39 TX((medication* OR medicine* OR drug* OR chemotherap* OR "chemo-therap*" OR prescription* OR prescrib* OR pharmac* OR dose* OR dosage* OR dosing OR agent* OR dispens*) N3 (error* OR mistake* OR incident*)) 44
S38 S5 AND S16 AND S37 296
S37 S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 8,638
S36 TX("time trade off*" OR "time tradeoff*" OR tto OR timetradeoff*) 634
S35 TX("standard gamble*") 325
S34 TX(sf20 OR "sf 20" OR "sf twenty" OR sftwenty) 3
S33 TX(sf16 OR "sf 16" OR "sf sixteen" OR sfsixteen) 0
S32 TX(sf12 OR "sf 12" OR "sf twelve" OR sftwelve) 62
S31 TX(sf6* OR "sf 6*" OR "sf six*" OR sfsix* OR sf8 OR "sf 8" OR "sf eight" OR sfeight) 114
S30 TX(sf36* OR "sf 36*" OR "sf thirtysix*" OR "sf thirty six*") 434
S29 TX("short form*" OR shortform*) 330
S28 TX("euro qual" OR "euro qol" OR "euro qual5d" OR "euro qol5d" OR "eq-5d" OR "eq5-d" OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d) 1,077
S27 TX(hui OR hui1 OR hui2 OR hui3) 117
S26 TX(hye OR hyes) 36
S25 TX("health* year* equivalent*") 54
S24 TX(multiattribute* OR "multi attribute*") 429
S23 TX((index N3 wellbeing) OR (quality N3 wellbeing) OR qwb) 35
S22 TX("health state*" OR "health status" OR "illness state*" OR "illness status") 1,262
S21 TX(utility OR utilities OR disutility OR disutilities) 5,578
S20 TX(daly*) 406
S19 TX("disability adjusted life") 358
S18 TX(qaly* OR qald* OR qale* OR qtime*) 4,764
S17 TX("quality adjusted" OR "adjusted life year*") 6,330
S16 S8 OR S15 5,714
S15 S13 AND S14 5,521
S14 TX(medication* OR medicine* OR drug* OR chemotherap* OR "chemo-therap*" OR prescription* OR prescrib* OR pharmac* OR dose* OR dosage* OR dosing OR agent* OR dispens*) 23,331
S13 S9 OR S10 OR S11 OR S12 9,300
S12 TX("clinical incident*" OR "incident report*") 5

S11 TX("side effect*" OR harms) 542
S10 TX((adverse OR undesirable OR harm* OR serious OR critical OR safety) N3 (effect* OR incident* OR reaction* OR event* OR outcome*)) 4,532
S9 TX(complication*) 5,578
S8 S6 OR S7 366
S7 TX(ADE OR ADEs OR ADR OR ADRs OR AME OR AMEs OR AMR OR AMRs) 72
S6 TX(toxicity) 297
S5 S1 OR S2 OR S3 OR S4 13,940
S4 TX(ward or wards) 430
S3 TX(admission* OR admitted) 2,291
S2 TX((acute OR secondary OR tertiary) N2 (care OR healthcare OR setting*)) 1,054
S1 TX(hospital* OR inpatient* OR "in-patient") 13,243

A.7: Source: Cost-Effectiveness Analysis (CEA) Registry

Interface / URL: https://research.tufts-nemc.org/cear4/Home.aspx
Search date: 09/06/14
Retrieved records: 1 (2 results, 1 excluded as duplicate of record already in the results Endnote Library)
Search strategy:

Basic search interface used. Following terms searched on individually. Only results with publication date of 2007 to date retrieved.

adverse drug = 2
adverse drugs = 0
adverse medication = 0
adverse medications = 0
adverse medicine = 0
adverse medicines = 0
drug error = 0
drugs error = 0
drugs error = 0
drugs errors = 0
medication error = 0 (1 duplicate of above retrieved)
medication errors = 0 (1 duplicate of above retrieved)
medications error = 0
medications errors =
medicine error = 0
medicine errors = 0
medicines error = 0
medicines errors = 0
prescription error = 0
prescription errors = 0
prescriptions error = 0
prescriptions errors = 0
prescribing error = 0
prescribing errors = 0
pharmacy error = 0
pharmacy errors = 0
dose error = 0
dose errors = 0
doses error = 0
doses errors = 0
dosage error = 0
dosage errors = 0
dosages error = 0
dosages errors = 0
dosing error = 0
dosing errors = 0

dispensary error = 0
dispensary errors = 0
dispensing error = 0
dispensing errors= 0
mistake = 0
mistakes = 0

A.8: Source: ScHARRHUD (Health Utilities Database)

Interface / URL: http://update-sbs.update.co.uk/scharr11/index.php?recordsN1&m=search
Search date: 09/06/14
Retrieved records: 39
Search strategy:

1 (hospital* or inpatient* or in-patient) 93
2 (acute care or acute healthcare or acute health care or acute setting* or secondary care or secondary healthcare or secondary health care or secondary setting* or tertiary care or tertiary healthcare or tertiary health care or tertiary setting*) 6
3 (admission* or admitted) 24
4 (ward or wards) 3
5 (#1 OR #2 OR #3 OR #4) 100
6 toxicity 1
7 (ADE or ADEs or ADR or ADRs or AME or AMEs or AMR or AMRs) 3
8 (complication* or adverse or undesirable or harm* or safety or side effect*) 105
9 ((serious or critical) and (effect* or incident* or reaction* or event* or outcome*)) 13
10 (side effect* or harms) 5
11 (clinical incident* or incident report*) 0
12 (#6 OR #7 OR #8 OR #9 OR #10 OR #11) 113
13 (#5 AND #12) 36
14 ((medication* or medicine* or drug* or chemotherap* or chemo-therap* or prescription* or prescrib* or pharmac* or dose* or dosage* or dosing or agent* or dispens*) and (error* or mistake* or incident*)) 3
15 (#13 OR #14) 39
16 #15 AND 2007 > 2014:YR 39

APPENDIX B

Excluded Studies at Full Paper Review

Table B.1: Papers excluded after full paper assessment

Study reference	Reason for exclusion
Avery AJ, Rodgers S, Cantrill JA, Armstrong S, Cresswell K, Eden M, et al. A pharmacist-led information technology intervention for medication errors (PINCER): a multicentre, cluster randomised, controlled trial and cost-effectiveness analysis Lancet [Internet]. 2012; (9823):[1310-9 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/cleed/articles/NHSEED-22012016211/frame.html.	No utilities reported
Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst. 2009 Dec 2;101(23):1624-32. PubMed PMID: 19920223. Pubmed Central PMCID: PMC2786917. English.	Utilities not related to adverse drug events
Bastani P, Kiadaliri AA. Cost-utility analysis of adjuvant therapies for breast cancer in Iran. Int J Technol Assess Health Care. 2012 April;28(2):110-4. PubMed PMID: 2012263556. English.	Utilities not related to adverse drug events
Berg J, Sauriol L, Connolly S, Lindgren P. Cost-effectiveness of dronedarone in patients with atrial fibrillation in the ATHENA trial. Can J Cardiol. 2013 Oct;29(10):1249-55. PubMed PMID: 23623647. English.	Utilities not related to adverse drug events
Best JH, Rubin RR, Peyrot M, Li Y, Yan P, Malloy J, et al. Weight-related quality of life, health utility, psychological well-being, and satisfaction with exenatide once weekly compared with sitagliptin or pioglitazone after 26 weeks of treatment. Diabetes Care. 2011 February;34(2):314-9. PubMed PMID: 2011099554. English.	Utilities not related to adverse drug events
Cadth. Medication reconciliation at discharge: a review of the clinical evidence and guidelines 2012; (4). Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32012000668/frame.html.	No utilities reported
Carr HJ, McDermott A, Tadbiri H, Uebbing AM, Londrigan M. The effectiveness of computer-based learning in hospitalized adults with heart failure on knowledge, re-admission, self-care, quality of life, and patient satisfaction: A systematic review protocol. JBI Database of Systematic Reviews and Implementation Reports. 2013;11(8):129-45. PubMed PMID: 2013577210. English.	Protocol (no results)
Casciano R, Chulikavit M, Perrin A, Liu Z, Wang X, Garrison LP. Cost-effectiveness of everolimus vs sunitinib in treating patients with advanced, progressive pancreatic neuroendocrine tumors in the United States. J Med Econ. 2012;15 Suppl 1:55-64. PubMed PMID: 22881362. English.	Utilities not related to adverse drug events
Chan DC, Chen JH, Wen CJ, Chiu LS, Wu SC. Effectiveness of the medication safety review clinics for older adults prescribed multiple medications. J Formos Med Assoc. 2014;113(2):106-13. PubMed PMID: 2014117198. English.	No utilities reported
Demsey J, Wright MD. Pyxis and medDISPENSE automated medication dispensing systems: a review of the clinical benefits and harms, cost-effectiveness, and guidelines for use 2009; (4). Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32011001207/frame.html.	No utilities reported
de Rezende BA, Or Z, Com-Ruelle L, Michel P. Economic evaluation in patient safety: a literature review of methods. BMJ Qual Saf. 2012 Jun;21(6):457-65. PubMed PMID: 22396602. English.	Review – included studies were assessed for relevence
Elliott RA, Putman KD, Franklin M, Annemans L, Verhaeghe N, Eden M, et al. Cost Effectiveness of a Pharmacist-Led Information Technology Intervention for Reducing Rates of Clinically Important Errors in Medicines Management in General Practices (PINCER). Pharmacoeconomics. 2014 Jun;32(6):573-90. PubMed PMID:	Utilities not related to adverse drug events

24639038. English.	
Fick DM, Mion LC, Beers MH, J LW. Health outcomes associated with potentially inappropriate medication use in older adults. Research in nursing & health. 2008 Feb;31(1):42-51. PubMed PMID: 18163447. English.	No utilities reported
Gates S, Perkins GD, Lamb SE, Kelly C, Thickett DR, Young JD, et al. Beta-Agonist Lung injury TrIal-2 (BALTI-2): a multicentre, randomised, double-blind, placebo-controlled trial and economic evaluation of intravenous infusion of salbutamol versus placebo in patients with acute respiratory distress syndrome. Health Technology Assessment (Winchester, England). 2013 Sep;17(38):v-vi, 1-87. PubMed PMID: 24028755. English.	Utilities not related to adverse drug events
Goodacre S.W. *et al*. Health utility after emergency medical admission: a cross-sectional survey. Health and Quality of Life Outcomes.10:20. English.	Utilities not related to adverse drug events
Grosso AM, Bodalia PN, MacAllister RJ, Hingorani AD, Moon JC, Scott MA. Comparative clinical- and cost-effectiveness of candesartan and losartan in the management of hypertension and heart failure: A systematic review, meta- and cost-utility analysis. Int J Clin Pract. 2011 March;65(3):253-63. PubMed PMID: 2011095396. English.	Utilities not related to adverse drug events
Hoffman DA, Debattista C, Valuck RJ, Iosifescu DV. Measuring severe adverse events and medication selection using a "PEER Report" for nonpsychotic patients: a retrospective chart review. Neuropsychiatr. 2012;8:277-84. PubMed PMID: 22802691. Pubmed Central PMCID: PMC3395405. English.	No utilities reported
Hong SH, Liu J, Tak S, Vaidya V. The impact of patient knowledge of patient-centered medication label content on quality of life among older adults. Res Social Adm Pharm. 2013 Jan-Feb;9(1):37-48. PubMed PMID: 22554393. English.	Utilities not related to adverse drug events
Keers RN, Williams SD, Cooke J, Ashcroft DM. Causes of medication administration errors in hospitals: a systematic review of quantitative and qualitative evidence. Drug Saf. 2013 Nov;36(11):1045-67. PubMed PMID: 23975331. Pubmed Central PMCID: PMC3824584. English.	Utilities not related to adverse drug events
Knapp M, Windmeijer F, Brown J, Kontodimas S, Tzivelekis S, Haro JM, et al. Cost-utility analysis of treatment with olanzapine compared with other antipsychotic treatments in patients with schizophrenia in the pan-European SOHO study. Pharmacoeconomics. 2008;26(4):341-58. PubMed PMID: 2008156891. English.	Utilities not related to adverse drug events
V. Kumar, S. Shenoy and A. Pai 2013 A prospective study of the drug prescribing pattern and assessment of adverse drug reactions in patients with idiopathic parkinson's disease in a tertiary care hospital	No utilities reported
Mira JJ, Navarro I, Botella F, Borras F, Nuno-Solinis R, Orozco D, et al. A Spanish pillbox app for elderly patients taking multiple medications: randomized controlled trial. J Med Internet Res. 2014;16(4):e99. PubMed PMID: 24705022. Pubmed Central PMCID: PMC4004137. English.	No utilities reported
Olsson IN, Runnamo R, Engfeldt P. Medication quality and quality of life in the elderly, a cohort study. Health Qual Life Outcomes. 2011;9:95. PubMed PMID: 22054205. Pubmed Central PMCID: PMC3216839. English.	Utilities not related to adverse drug events
Pelliciotti JdSS, Kimura M. Medications errors and health-related quality of life of nursing professionals in intensive care units. Rev Lat Am Enfermagem. 2010 Nov-Dec;18(6):1062-9. PubMed PMID: 21340269. English.	Utilities related to healthcare professionals involved in errors, rather than patients
Perras C *et al.* Technologies to reduce errors in dispensing and administration of medication in hospitals: clinical and economic analyses 2009; (4). Available from: http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32006000370/frame.html.	No utilities reported

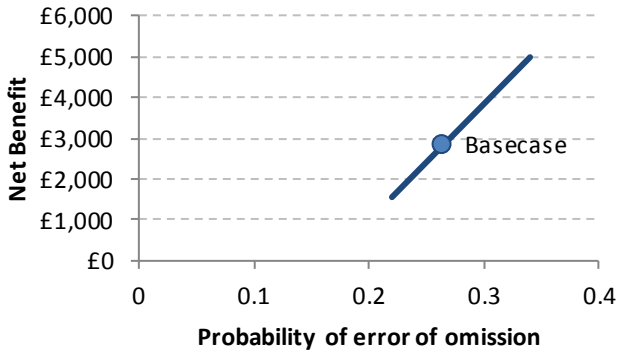
Rosery H, Bergemann R, Marx SE, Boehnke A, Melnick J, Sterz R, et al. Health-economic comparison of paricalcitol, calcitriol and alfacalcidol for the treatment of secondary hyperparathyroidism during haemodialysis. Clin Drug Investig. 2006;26(11):629-38. PubMed PMID: 17163297. English.	Utilities not related to adverse drug events
Saleh F, Mumu SJ, Ara F, Hafez MA, Ali L. Non-adherence to self-care practices & medication and health related quality of life among patients with type 2 diabetes: a cross-sectional study. BMC Public Health. 2014;14:431. PubMed PMID: 24885315. Pubmed Central PMCID: PMC4019601. English.	Utilities not related to adverse drug events
Smith KJ, Wateska A, Nowalk MP, Raymund M, Lee BY, Zimmerman RK, et al. Cost-effectiveness of procalcitonin-guided antibiotic use in community acquired pneumonia. J Gen Intern Med. 2013 Sep;28(9):1157-64. PubMed PMID: 23463457. Pubmed Central PMCID: PMC3744292 [Available on 09/01/14]. English.	Utilities not related to adverse drug events
Sperandio da Silva GM, Chambela MC, Sousa AS, Sangenis LHC, Xavier SS, Costa AR, et al. Impact of pharmaceutical care on the quality of life of patients with Chagas disease and heart failure: randomized clinical trial. Trials. 2012;13:244. PubMed PMID: 23270509. Pubmed Central PMCID: PMC3543334. English.	Protocol (no results)
Sowmya SKR, Thomas D, Zachariah S, Daniel Sunad A. Assessment of adverse events and quality of life of cancer patients in a secondary level care, rural hospital in South India. Value in Health Regional Issues. 2013 May;2(1):103-6. PubMed PMID: 2013289572. English.	Utilities not related to adverse drug events
Turner JP, Shakib S, Singhal N, Hogan-Doran J, Prowse R, Johns S, et al. Prevalence and factors associated with polypharmacy in older people with cancer. Support Care Cancer. 2014 Jul;22(7):1727-34. PubMed PMID: 24584682. English.	Utilities not related to adverse drug events
Ul-Haq Z, Mackay DF, Pell JP. Association between self-reported general and mental health and adverse outcomes: A retrospective cohort study of 19 625 Scottish adults. PLoS ONE. 2014 04 Apr;9(4). PubMed PMID: 2014290148. English.	Utilities not related to adverse drug events
Zhou M, Holden L, Bedard G, Zeng L, Lam H, Chu D, et al. The utilization of telephone follow-up in the advanced cancer population: A review of the literature. Journal of Comparative Effectiveness Research. 2012 November;1(6):509-17. PubMed PMID: 2012695209. English.	Opinion paper

APPENDIX C

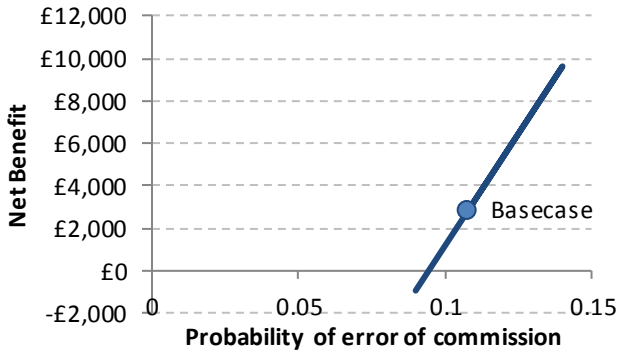
Univariate sensitivity analysis graphs

C.1: Baseline error rates

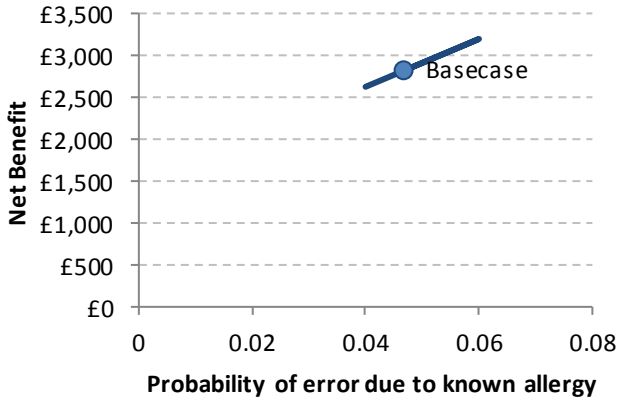
Error of omission



Error of commission

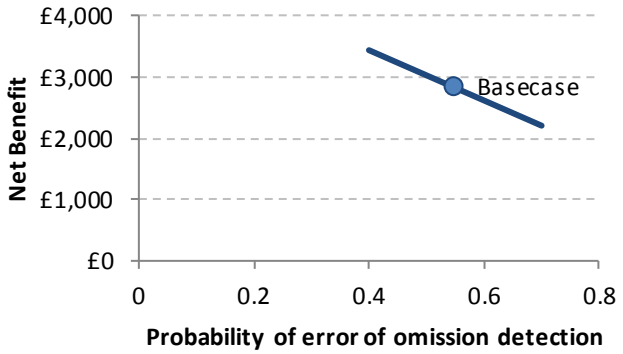


Error due to known allergy



C.2: Prescription error detection probabilities

Error of omission



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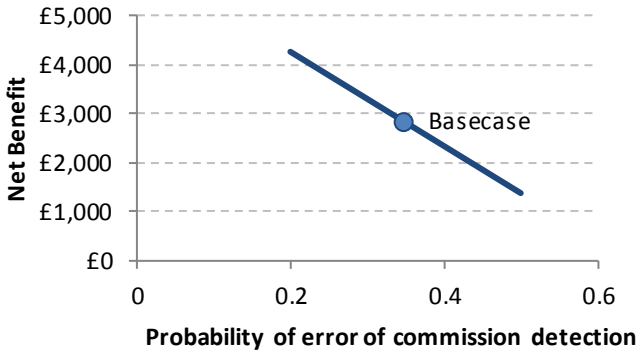

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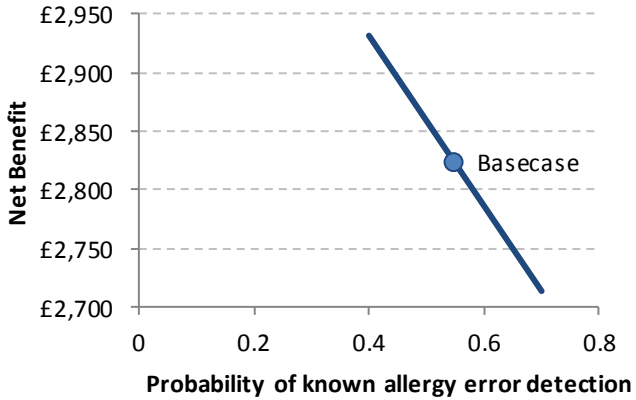
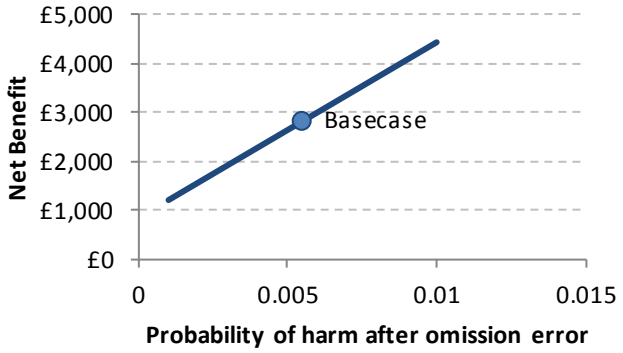


C.3: Probability of harm for undetected errors

Error of omission



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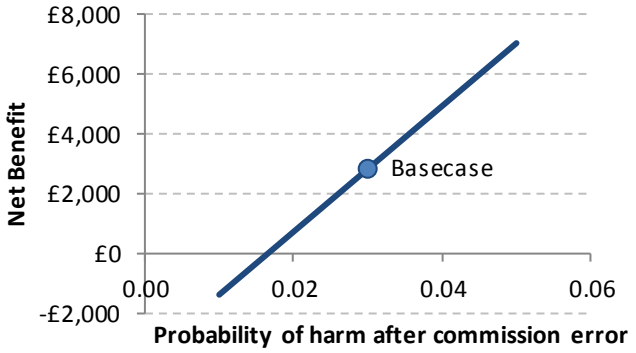

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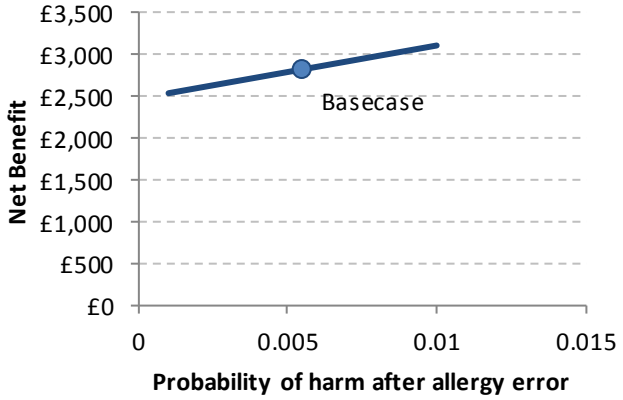
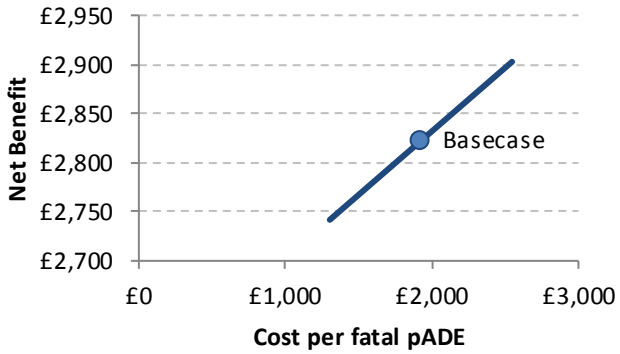
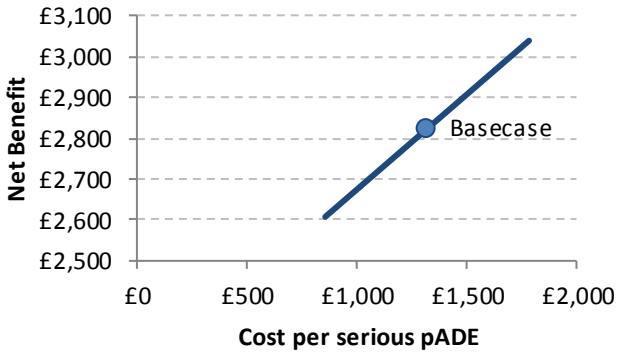


C.4: Cost of medication errors

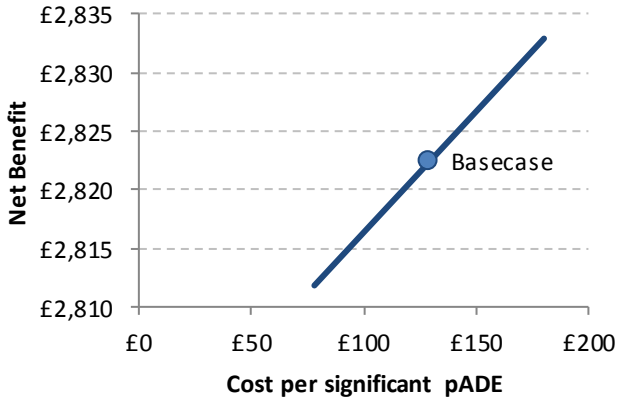
Cost of fatal or life-threatening pADE



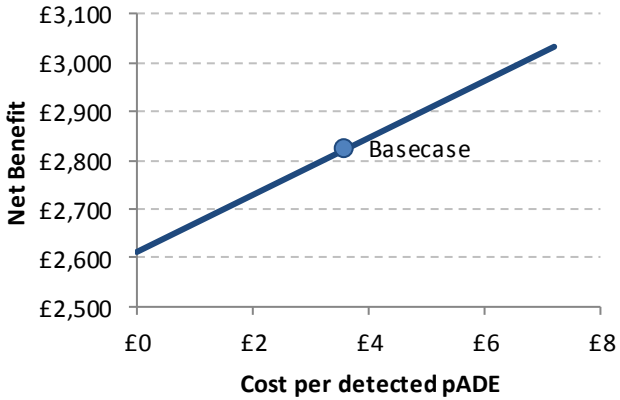
Cost of serious pADE



Cost of significant pADE

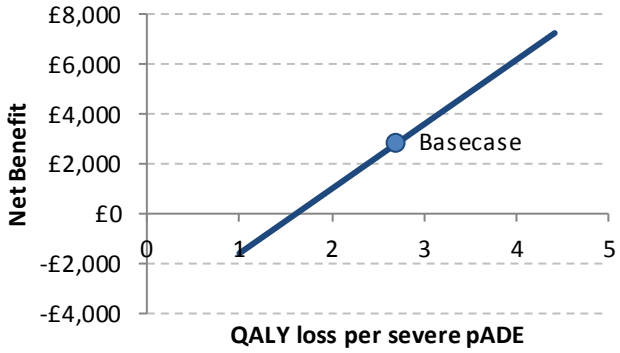


Cost of detected medication error

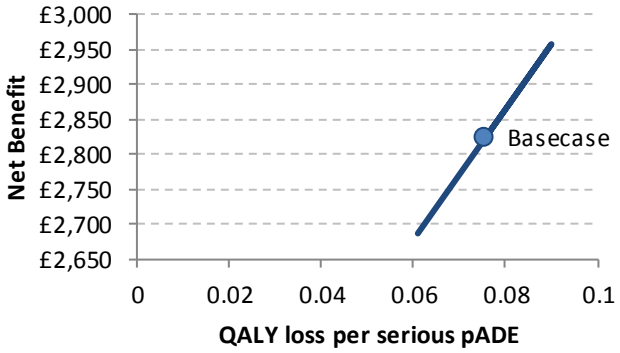


C.5: QALY loss from pADEs

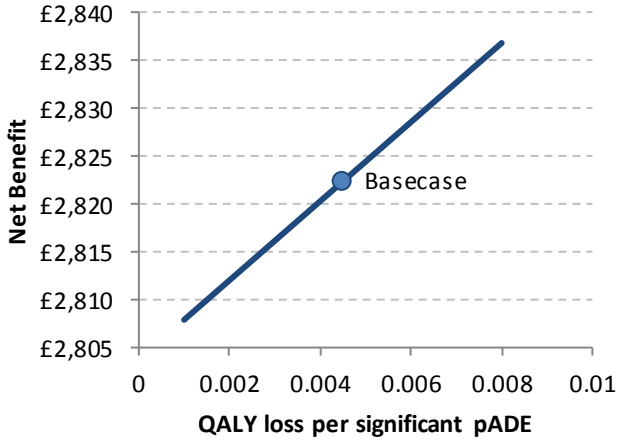
QALY loss of fatal or life threatening pADE



QALY loss of serious pADE



QALY loss of significant pADE



APPENDIX D

Two-way sensitivity analysis graphs

D.1: Cost and proportion of significant pADEs

Cost of signnificant pADE	Proportion of significant pADE										
	0.00	0.05	0.10	0.15	0.21	0.26	0.31	0.36	0.41	0.46	0.51
£78	£12,825	£12,811	£12,796	£12,782	£12,768	£12,753	£12,739	£12,724	£12,710	£12,695	£12,681
£90	£12,825	£12,810	£12,794	£12,778	£12,762	£12,747	£12,731	£12,715	£12,700	£12,684	£12,668
£100	£12,825	£12,809	£12,792	£12,775	£12,758	£12,741	£12,725	£12,708	£12,691	£12,674	£12,658
£115	£12,825	£12,807	£12,789	£12,770	£12,752	£12,733	£12,715	£12,697	£12,678	£12,660	£12,642
£130	£12,825	£12,805	£12,785	£12,765	£12,745	£12,725	£12,705	£12,685	£12,666	£12,646	£12,626
£145	£12,825	£12,804	£12,782	£12,761	£12,739	£12,717	£12,696	£12,674	£12,653	£12,631	£12,610
£160	£12,825	£12,802	£12,779	£12,756	£12,733	£12,709	£12,686	£12,663	£12,640	£12,617	£12,594
£170	£12,825	£12,801	£12,777	£12,753	£12,728	£12,704	£12,680	£12,656	£12,631	£12,607	£12,583
£180	£12,825	£12,800	£12,775	£12,749	£12,724	£12,699	£12,673	£12,648	£12,623	£12,598	£12,573

D.2: Cost and proportion of serious pADEs

Cost of serious pADE	Proportion of serious pADE										
	0.00	0.08	0.16	0.25	0.33	0.41	0.49	0.57	0.66	0.74	0.82
£856	£15,741	£15,210	£14,700	£14,209	£13,736	£13,281	£12,841	£12,417	£12,008	£11,612	£11,230
£900	£15,741	£15,199	£14,678	£14,176	£13,693	£13,227	£12,778	£12,345	£11,927	£11,523	£11,132
£1,000	£15,741	£15,173	£14,627	£14,101	£13,595	£13,107	£12,636	£12,183	£11,744	£11,321	£10,912
£1,100	£15,741	£15,147	£14,576	£14,026	£13,497	£12,986	£12,495	£12,020	£11,562	£11,119	£10,691
£1,200	£15,741	£15,121	£14,525	£13,951	£13,399	£12,866	£12,353	£11,857	£11,379	£10,917	£10,470
£1,300	£15,741	£15,095	£14,474	£13,876	£13,300	£12,746	£12,211	£11,695	£11,196	£10,715	£10,250
£1,400	£15,741	£15,069	£14,423	£13,801	£13,202	£12,625	£12,069	£11,532	£11,014	£10,513	£10,029
£1,500	£15,741	£15,043	£14,372	£13,726	£13,104	£12,505	£11,927	£11,370	£10,831	£10,311	£9,808
£1,600	£15,741	£15,017	£14,321	£13,651	£13,006	£12,385	£11,785	£11,207	£10,648	£10,109	£9,587
£1,700	£15,741	£14,991	£14,270	£13,576	£12,908	£12,264	£11,643	£11,044	£10,466	£9,907	£9,367
£1,781	£15,741	£14,970	£14,229	£13,516	£12,829	£12,167	£11,529	£10,913	£10,318	£9,744	£9,188

D.3: Cost and proportion of severe pADEs

Cost of severe pADE	Proportion of severe pADE										
	0.00	0.04	0.08	0.12	0.16	0.20	0.24	0.28	0.32	0.36	0.40
£1,302	£143,341	£48,369	£28,941	£20,569	£15,906	£12,934	£10,875	£9,363	£8,207	£7,294	£6,555
£1,400	£143,341	£48,345	£28,912	£20,538	£15,874	£12,901	£10,841	£9,330	£8,173	£7,260	£6,520
£1,600	£143,341	£48,296	£28,853	£20,475	£15,808	£12,834	£10,773	£9,261	£8,104	£7,190	£6,450
£1,800	£143,341	£48,248	£28,794	£20,412	£15,743	£12,767	£10,705	£9,192	£8,034	£7,120	£6,379
£2,000	£143,341	£48,199	£28,735	£20,348	£15,677	£12,700	£10,637	£9,123	£7,965	£7,050	£6,309
£2,200	£143,341	£48,150	£28,677	£20,285	£15,612	£12,633	£10,569	£9,054	£7,895	£6,980	£6,239
£2,400	£143,341	£48,101	£28,618	£20,222	£15,546	£12,566	£10,501	£8,985	£7,826	£6,910	£6,168
£2,500	£143,341	£48,077	£28,588	£20,191	£15,513	£12,533	£10,467	£8,951	£7,791	£6,875	£6,133
£2,544	£143,341	£48,066	£28,575	£20,177	£15,499	£12,518	£10,452	£8,936	£7,776	£6,860	£6,118

D.4: QALY loss and proportion of significant pADEs

QALY loss of significant pADE	Proportion of significant pADE										
	0.00	0.05	0.10	0.15	0.21	0.26	0.31	0.36	0.41	0.46	0.51
0.0010	£12,825	£12,810	£12,795	£12,780	£12,765	£12,750	£12,735	£12,719	£12,704	£12,689	£12,674
0.0015	£12,825	£12,810	£12,794	£12,778	£12,762	£12,746	£12,730	£12,715	£12,699	£12,683	£12,667
0.0020	£12,825	£12,809	£12,792	£12,776	£12,759	£12,743	£12,726	£12,710	£12,693	£12,677	£12,660
0.0025	£12,825	£12,808	£12,791	£12,774	£12,757	£12,739	£12,722	£12,705	£12,688	£12,671	£12,654
0.0030	£12,825	£12,808	£12,790	£12,772	£12,754	£12,736	£12,718	£12,700	£12,683	£12,665	£12,647
0.0035	£12,825	£12,807	£12,788	£12,770	£12,751	£12,733	£12,714	£12,696	£12,677	£12,659	£12,640
0.0040	£12,825	£12,806	£12,787	£12,768	£12,749	£12,729	£12,710	£12,691	£12,672	£12,653	£12,634
0.0050	£12,825	£12,805	£12,784	£12,764	£12,743	£12,723	£12,702	£12,681	£12,661	£12,641	£12,620
0.0060	£12,825	£12,803	£12,782	£12,760	£12,738	£12,716	£12,694	£12,672	£12,650	£12,628	£12,607
0.0070	£12,825	£12,802	£12,779	£12,755	£12,732	£12,709	£12,686	£12,663	£12,639	£12,616	£12,593
0.0080	£12,825	£12,801	£12,776	£12,751	£12,727	£12,702	£12,678	£12,653	£12,629	£12,604	£12,580

D.5: QALY loss and proportion of serious pADEs

QALY loss of serious pADE	Proportion of serious pADE										
	0.00	0.08	0.16	0.25	0.33	0.41	0.49	0.57	0.66	0.74	0.82
0.0610	£15,741	£15,148	£14,573	£14,016	£13,476	£12,952	£12,443	£11,950	£11,470	£11,004	£10,551
0.0640	£15,741	£15,136	£14,551	£13,984	£13,436	£12,905	£12,390	£11,890	£11,406	£10,936	£10,479
0.0680	£15,741	£15,120	£14,521	£13,942	£13,383	£12,842	£12,319	£11,812	£11,321	£10,846	£10,385
0.0720	£15,741	£15,104	£14,491	£13,900	£13,330	£12,780	£12,248	£11,735	£11,238	£10,758	£10,293
0.0760	£15,741	£15,089	£14,462	£13,859	£13,278	£12,718	£12,179	£11,658	£11,156	£10,671	£10,202
0.0800	£15,741	£15,073	£14,432	£13,817	£13,226	£12,657	£12,110	£11,583	£11,075	£10,585	£10,113
0.0840	£15,741	£15,058	£14,403	£13,776	£13,174	£12,597	£12,042	£11,509	£10,996	£10,501	£10,025
0.0880	£15,741	£15,042	£14,374	£13,735	£13,123	£12,537	£11,975	£11,435	£10,917	£10,419	£9,939
0.0900	£15,741	£15,034	£14,359	£13,715	£13,098	£12,508	£11,942	£11,399	£10,878	£10,378	£9,896

D.6: QALY loss and proportion of severe pADEs

QALY loss of severe pADE	Proportion of severe pADE										
	0.00	0.04	0.08	0.12	0.16	0.20	0.24	0.28	0.32	0.36	0.40
1.0000	£143,341	£82,596	£57,674	£44,103	£35,566	£29,700	£25,422	£22,163	£19,598	£17,527	£15,820
1.3000	£143,341	£73,389	£49,004	£36,601	£29,091	£24,055	£20,443	£17,727	£15,609	£13,912	£12,522
1.6000	£143,341	£66,029	£42,600	£31,281	£24,610	£20,213	£17,095	£14,770	£12,969	£11,534	£10,362
1.9000	£143,341	£60,011	£37,677	£27,311	£21,326	£17,429	£14,690	£12,659	£11,093	£9,850	£8,837
2.2000	£143,341	£54,998	£33,773	£24,235	£18,815	£15,319	£12,878	£11,076	£9,692	£8,595	£7,704
2.5000	£143,341	£50,758	£30,603	£21,782	£16,833	£13,665	£11,463	£9,845	£8,604	£7,623	£6,828
2.8000	£143,341	£47,125	£27,976	£19,780	£15,228	£12,333	£10,329	£8,860	£7,736	£6,849	£6,131
3.1000	£143,341	£43,977	£25,765	£18,115	£13,903	£11,238	£9,399	£8,054	£7,027	£6,218	£5,563
3.4000	£143,341	£41,224	£23,878	£16,708	£12,791	£10,321	£8,623	£7,383	£6,437	£5,693	£5,092
3.7000	£143,341	£38,794	£22,248	£15,504	£11,843	£9,543	£7,965	£6,815	£5,939	£5,250	£4,694
4.4100	£143,341	£34,047	£19,155	£13,246	£10,075	£8,098	£6,747	£5,765	£5,019	£4,433	£3,961

D.7: QALY loss and cost of significant pADEs

		QALY loss of significant pADE										
		0.001	0.002	0.002	0.003	0.003	0.004	0.004	0.005	0.006	0.007	0.008
Cost of signnificant pADE	£78	£12,777	£12,774	£12,770	£12,767	£12,763	£12,760	£12,757	£12,750	£12,743	£12,736	£12,729
	£90	£12,771	£12,767	£12,764	£12,760	£12,757	£12,754	£12,750	£12,743	£12,737	£12,730	£12,723
	£100	£12,765	£12,762	£12,758	£12,755	£12,752	£12,748	£12,745	£12,738	£12,731	£12,724	£12,718
	£115	£12,757	£12,754	£12,750	£12,747	£12,744	£12,740	£12,737	£12,730	£12,723	£12,716	£12,710
	£130	£12,749	£12,746	£12,742	£12,739	£12,736	£12,732	£12,729	£12,722	£12,715	£12,708	£12,702
	£145	£12,741	£12,738	£12,734	£12,731	£12,728	£12,724	£12,721	£12,714	£12,707	£12,700	£12,694
	£160	£12,733	£12,730	£12,726	£12,723	£12,720	£12,716	£12,713	£12,706	£12,699	£12,692	£12,686
	£170	£12,728	£12,724	£12,721	£12,718	£12,714	£12,711	£12,707	£12,701	£12,694	£12,687	£12,680
	£180	£12,722	£12,719	£12,716	£12,712	£12,709	£12,705	£12,702	£12,695	£12,689	£12,682	£12,675

D.7: QALY loss and cost of serious pADEs

		QALY loss of serious pADE								
		0.061	0.064	0.068	0.072	0.076	0.080	0.084	0.088	0.090
Cost of serious pADE	£856	£13,517	£13,467	£13,402	£13,337	£13,273	£13,209	£13,146	£13,084	£13,053
	£900	£13,462	£13,413	£13,348	£13,283	£13,219	£13,156	£13,093	£13,031	£13,000
	£1,000	£13,340	£13,291	£13,226	£13,162	£13,099	£13,036	£12,974	£12,913	£12,882
	£1,100	£13,217	£13,169	£13,105	£13,041	£12,979	£12,917	£12,855	£12,794	£12,764
	£1,200	£13,095	£13,047	£12,983	£12,921	£12,858	£12,797	£12,736	£12,675	£12,645
	£1,300	£12,972	£12,925	£12,862	£12,800	£12,738	£12,677	£12,617	£12,557	£12,527
	£1,400	£12,850	£12,803	£12,740	£12,679	£12,618	£12,557	£12,498	£12,438	£12,409
	£1,500	£12,727	£12,681	£12,619	£12,558	£12,498	£12,438	£12,378	£12,320	£12,291
	£1,600	£12,605	£12,558	£12,497	£12,437	£12,377	£12,318	£12,259	£12,201	£12,172
	£1,700	£12,482	£12,436	£12,376	£12,316	£12,257	£12,198	£12,140	£12,082	£12,054
	£1,781	£12,383	£12,338	£12,278	£12,218	£12,160	£12,101	£12,044	£11,987	£11,958

D8: QALY loss and cost of severe pADEs

Cost of severe pADE	QALY loss of severe pADE										
	1.00	1.30	1.60	1.90	2.20	2.50	2.80	3.10	3.40	3.70	4.41
£1,302	£30,186	£24,448	£20,543	£17,714	£15,570	£13,888	£12,535	£11,422	£10,490	£9,699	£8,230
£1,400	£30,109	£24,386	£20,491	£17,669	£15,530	£13,853	£12,503	£11,393	£10,464	£9,675	£8,209
£1,600	£29,953	£24,259	£20,385	£17,577	£15,449	£13,781	£12,438	£11,334	£10,409	£9,624	£8,167
£1,800	£29,796	£24,133	£20,278	£17,485	£15,369	£13,709	£12,373	£11,274	£10,355	£9,574	£8,124
£2,000	£29,640	£24,006	£20,172	£17,394	£15,288	£13,637	£12,308	£11,215	£10,300	£9,524	£8,081
£2,200	£29,484	£23,879	£20,065	£17,302	£15,207	£13,565	£12,243	£11,156	£10,246	£9,473	£8,039
£2,400	£29,327	£23,753	£19,959	£17,210	£15,127	£13,493	£12,178	£11,097	£10,192	£9,423	£7,996
£2,500	£29,249	£23,689	£19,906	£17,164	£15,086	£13,457	£12,146	£11,067	£10,165	£9,398	£7,975
£2,544	£29,214	£23,661	£19,882	£17,144	£15,068	£13,441	£12,131	£11,054	£10,153	£9,387	£7,965