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Death audits and reviews for reducing maternal, perinatal and child mortality (Protocol)

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[Intervention Protocol]

Death audits and reviews for reducing maternal, perinatal and child mortality

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the impact and cost-effectiveness of different types of death review in reducing maternal, perinatal and child mortality.

BACKGROUND

Description of the condition

'Maternal mortality' is defined as the death of a woman during pregnancy or within 42 days of delivery, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes (WHO 2004). 'Perinatal mortality' is defined as the stillbirth or death of a newborn baby within the first seven days of life (WHO 2006). 'Child mortality' is defined as the death of a child under the age of five years (UNICEF 2015). The maternal mortality ratio and child mortality rate are expressed per 100,000 live births (UNICEF 2015; WHO 2014). The perinatal mortality rate is expressed per 1000 total births (WHO 2006).

The United Nations' Sustainable Development Goals include reducing the global maternal mortality ratio to less than 70 per 100,000 live births and ending preventable deaths of newborns and children under five years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and mortality in children aged less than five years to at least as low as 25 per 1000 live births, by 2030 (UN 2017). Although progress is being made towards achieving these goals, it is not fast enough, especially in low-income countries (Wang 2014; WHO 2014). The absolute number of maternal, child and perinatal deaths, and the corresponding death rates, are higher in Africa than in any other region. In 2015, there were an estimated

303,000 maternal deaths globally, 99% of which were in low- and middle-income countries, and 66% in sub-Saharan Africa alone (WHO 2015). In 2016, there were an estimated 5,642,000 child deaths globally, more than half of which occurred in sub-Saharan Africa (UNICEF 2017).

Description of the intervention

'Death audit and review' is a broad term intended to include every different method of reviewing deaths, which we define as not only identifying the medical cause of death, but also identifying avoidable factors and making recommendations for avoiding such deaths in the future. The principle methods used are community-based audit (verbal and social autopsy), facility-based audits (significant event analysis (SEA)) and a combination of both (confidential enquiry).

In low-income countries without comprehensive death registration, deaths in the community are often investigated using verbal autopsy. The family of the deceased is interviewed according to a standard questionnaire (developed by WHO 2007), and the information is then interpreted by physicians or by a computer to ascertain the most likely medical cause of death (Waiswa 2010). However, there is usually no attempt to identify avoidable factors as it is assumed that it is already known which interventions are needed to tackle each principle disease. Verbal autopsy has been incorporated into wider health and demographic surveillance strategies (Adazu 2005), although its accuracy has been questioned due to the non-specific nature of signs and symptoms that may not be easily observed or remembered at interview (Butler 2010; Sloan 2001; Waiswa 2010). Social autopsy was designed as an add-on to verbal autopsy, and indeed the two are sometimes combined as a 'verbal and social autopsy' (VASA) (Kalter 2011). The aim is to make a 'social diagnosis', identifying avoidable factors prior to death in the home and community, within health facilities and at different stages of the patient pathway. In India this has been used in a participatory manner, which has been termed social audit for community action (SACA) (Nandan 2005). In this method, the community is asked to identify causes of death and avoidable factors. In this review we will not include studies investigating stand-alone verbal autopsy (whether conducted by a physician or a computer) with the sole purpose of identifying the medical cause of death.

Death audits in health facilities are usually based on SEA. This is an important part of revalidation for doctors in the UK, and the Royal College of General Practitioners (RCGP 2014) recommends that "SEA team discussions should be a routine part of your practice's quality improvement and clinical governance". Cases are usually discussed in a multidisciplinary team meeting (Hussein 2007). After discussing the details of the case, health workers identify avoidable factors and learning needs, and propose actions to be taken and changes to be made. The process does not intend to place blame, but the names of staff involved are not kept confidential. Indeed it is argued that "non-confidential straightforwardness and open-mindedness" are vital for a successful strategy (Supratikto 2002). A similar process occurs in 'mortality meetings', 'root cause analysis' meetings and, indeed, 'serious case reviews' (in child protection cases). Most mortality meetings take place at secondary healthcare facilities, drawing upon medical records to identify the diagnosis and key management interventions. Severe morbidity or near-miss reviews are also used to learn lessons; these review cases in which an individual almost died.

Confidential enquiry is the most comprehensive method by which to investigate deaths, because it considers not only the diagnosis and treatment in health facilities, but also the entire course of an illness and treatment-seeking pathway, to identify avoidable factors and to recommend changes at every level of the health and social care system and beyond, in order to prevent future deaths. This is particularly important in low-income countries where the majority of child deaths occur outside of any health facility (Breman 2001). A key feature of such enquiries is that the names of the individuals and any health workers involved are kept confidential, so that blame is avoided. These enquiries were pioneered in high-income countries, based entirely on written (usually medical) records examined by a multidisciplinary panel of experts, which includes not only health workers but also other professionals such as social services and the police (Lewis 2011; Pearson 2008). Such confidential enquiries have been useful for evaluating gaps in healthcare in the UK (Pearson 2008; WHO 2004), but are not yet widely used in low-income countries (Hussein 2007). The expert analysis involves both quantitative and qualitative elements. In the UK, all the included deaths were analysed quantitatively for basic information such as age, sex, socioeconomic status, location of death, time (seasonality) of death, and cause of death. Further detailed investigations were carried out on all maternal deaths and a subset of child deaths. A multidisciplinary panel reviewed each of these cases and identified avoidable factors. These were analysed thematically, illustrated by cases, and were used to generate recommendations as to how deaths might be avoided in future (Pearson 2008a).

How the intervention might work

Participation by communities in death audits is a strong basis for collective action to reduce mortality. In health facilities, significant event audit is a potentially powerful intervention to enable staff to learn from their mistakes and to institute important changes to procedures within their institution; the key mechanism is believed to be recommendation, then implementation of the proposed solutions (Pattinson 2009). The confidential enquiry approach is designed to identify avoidable factors at every step of the treatment-seeking pathway, and to make recommendations not only to improve the health system, but also to address avoidable factors outside of health facilities. Case review meetings, followed by the dissemination of recommendations to health workers, com-

munities, or both, are essentially aiming to change clinician and patient behaviour. There are many theories of behaviour change, but these have been synthesised and integrated into the theoretical domains framework, which consists of 14 domains (Cane 2012; Michie 2014). Many of these domains are addressed by death audit and review. Those participating in the death review meetings gain knowledge about avoidable factors. The recommendations often set goals, and progress towards these can be audited. Repetition of similar recommendations may help clinicians to better remember guidelines, whereas social pressure may encourage them to better follow these guidelines. Death review meetings may also change health workers' beliefs about the consequences of their actions: the knowledge that deaths will be investigated and reviewed may motivate them to avoid poor practice. Discussing deaths, especially of mothers and children, often evokes an emotional response, which usually motivates health workers and parents to do all they can to prevent such deaths.

Death reviews may conceivably have some adverse effects. First, there is a cost (time and financial) to conducting death reviews. In the community, field workers need to be employed to investigate cases. In health facilities, staff are taken away from frontline duties to review cases, which may have an adverse impact on the delivery of care. It has been argued that these resources should instead be spent directly on implementing interventions that are known to be effective (Koblinsky 2017). Second, if death reviews are not handled sensitively, they may lead to blaming, humiliation and demotivation of staff, which may in turn lead to poorer quality of care. Third, focus on only one level of care (such as a district hospital) may lead to the diversion of resources away from other levels of care (such as primary care facilities). Fourth, there is the potential for inaccuracy - reviews based on indirect information (especially at the community level) may be incomplete or inadequate at diagnosing the likely cause of death.

Why it is important to do this review

The World Health Organization recommends that health facilities should conduct maternal and perinatal death reviews (WHO 2013; WHO 2016). In general, there is an underlying assumption that death reviews are useful and will impact on mortality but there is little robust evidence to support this (Pattinson 2005). It would be useful for policy-makers to understand which type of death review has the greatest impact on maternal, perinatal and child death rates, and what the essential features of an effective death review process are. Although confidential enquiry seems to be the most comprehensive method for addressing the whole range of avoidable factors, and hence has the potential to have the greatest impact, it is unclear whether it could be adapted, whether it would be feasible or whether it would be effective in reducing mortality in low-income countries.There is no comprehensive systematic review in the literature examining the impact of the aforementioned methods of investigating deaths.

OBJECTIVES

To assess the impact and cost-effectiveness of different types of death review in reducing maternal, perinatal and child mortality.

METHODS

Criteria for considering studies for this review

Types of studies

We will include cluster randomised trials. However, as these are expensive and difficult to conduct, and large sample sizes are needed to measure impact on mortality, we therefore anticipate that we will find very few. We therefore will also include cluster non-randomised trials, studies with a step-wedge design, controlled before-and-after studies and interrupted time series studies.

For cluster randomised trials, cluster non-randomised trials and controlled before-and-after studies, we will use the Effective Practice and Organisation of Care (EPOC) criteria (EPOC 2017a) and will exclude studies with only one intervention or control site; for interrupted time series studies, we will exclude studies that do not have a clearly defined point in time when the intervention occurred and at least three data points before and three after the intervention.

Types of participants

Participants receiving the intervention (audits and reviews of deaths) can be health facilities of any level or the wider community, such as subdistricts or districts in which the policy is implemented, or both. Participants who should benefit from the intervention are pregnant women giving birth and their children at the study sites during the study period in which the outcomes are measured.

Types of interventions

We will include any form of death audit or review that involves studying individual cases of deaths, identifying avoidable factors, and making recommendations. We will classify the interventions as verbal and social autopsy, facility-based death audit and SEA, or confidential enquiry. We will not include verbal autopsy studies that evaluated only causes of death, and not avoidable factors. We will include studies of maternal, perinatal, newborn and child deaths, alone or in combination. We will not include severe morbidity or near-miss reviews. We will include comparisons of the same population before introduction of the death review, or other comparable communities in which the death review was not implemented.

Types of outcome measures

We plan to include studies in the review irrespective of whether measured outcome data are reported in a 'usable' way. We will include and describe in a 'Characteristics of included studies' table studies that meet the inclusion criteria.

Main outcomes

To be included in the review, a study will need to report at least one of the following outcomes:

- perinatal mortality rate;
- stillbirth rate;
- neonatal mortality rate;
- mortality rate in children under five years of age;
- maternal mortality ratio.

Secondary outcomes

For included studies, we will also consider other outcomes:

- outcomes relating to maternal severe morbidity, such as maternal near miss or as defined by authors;
- outcomes relating to quality of care in participating facilities;
- cost per death averted.

Search methods for identification of studies

Electronic searches

We will search the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- MEDLINE Ovid;
- Embase Ovid,
- Global Health Ovid;
- Global Health Library - Regional Indexes;
- Popline;
- CINAHL EBSCO Host (Cumulative Index to Nursing and Allied Health Literature Host);
- Science Citation Index, Web of Science Core Collection;
- Conference Proceedings Citation Index - Science, Web of Science Core Collection.

We provide a MEDLINE search strategy, with no language or publication date limits, in Appendix 1. We will adapt the MEDLINE strategy for use with all the other databases.

Searching other resources

We will identify ongoing studies through searches of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/). We will search Google and the websites of the World Bank and the WHO. We will identify relevant articles from the reference lists of articles found in these searches. We will contact experts in the field to advise us of unpublished or grey literature, and we will also search the two grey literature collections, OpenGrey and the Grey Literature Report.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management database and remove duplicates. Two review authors will independently screen titles and abstracts for inclusion. We will retrieve the full-text study reports/publications and two review authors will independently screen the full text, identify studies for inclusion, and identify and record the reasons for exclusion of ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third reviewer. We will list studies that initially appeared to meet the inclusion criteria but were later excluded, together with reasons for exclusion, in a 'Characteristics of excluded studies' table. We will collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will also provide any information we can obtain about ongoing studies. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009) and a 'Characteristics of excluded studies' table.

Data extraction and management

We will use a standard data collection form, adapted from the Cochrane good practice data collection form, for study characteristics and outcome data. We will first pilot this on at least one study in the review. Two review authors (MW, JP) will independently extract the following study characteristics from included studies.

1. Methods: study design, number of study centres and location, study setting, withdrawals, date of study, follow-up.
2. Participating health facilities: number, inclusion criteria, exclusion criteria, other relevant characteristics.
3. Interventions: intervention components, comparison, fidelity assessment.
4. Outcomes: main and other outcomes specified and collected, time points reported.
5. Notes: funding for trial, notable conflicts of interest of trial authors, ethical approval.

Two review authors (MW and JP) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table whether outcome data were reported in an unusable way. We will resolve disagreements by consensus or by involving a third review author (AH or AD).

Assessment of risk of bias in included studies

Two review authors (MW and JP) will independently assess the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the guidance from the EPOC group (EPOC 2017b). We will resolve any disagreement by discussion or by involving a third review author (AH or AD). We will assess the risk of bias according to the following domains.

Cluster randomised trial/cluster non-randomised trial/controlled before-and-after study criteria:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting;
- baseline outcomes measurement;
- baseline characteristics;
- other bias.

Interrupted time series study criteria:

- was the intervention independent of other changes?
- was the shape of the intervention effect prespecified?
- was the intervention unlikely to affect data collection?
- was knowledge of the allocated interventions adequately prevented during the study?
- were incomplete outcome data adequately addressed?
- was the study free from selective outcome reporting?
- was the study free from other risks of bias?

We will judge each potential source of bias as high, low or unclear, and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise our 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessments, risk of bias for all-cause mortality may be very different than for a participant-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table. We will not exclude studies on the grounds of their risk of bias, but will clearly report the risk of bias when presenting the results of the studies.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will estimate the effect of the intervention using risk ratios for dichotomous data, together with the appropriate associated 95% confidence intervals, and mean differences or standardised mean differences for continuous data, together with the 95% appropriate associated confidence intervals. We will ensure that an increase in scores for continuous outcomes can be interpreted in the same way for each outcome, explain the direction to the reader and report where the directions were reversed if this was necessary. For interrupted time series studies, we will estimate a standardised effect size for each study by dividing the level by the slope and the standard error by the standard deviation of the preintervention slope. We will enter the effect sizes for level and slope in Review Manager 5 (Cochrane 2014) using the generic inverse variance method (Ramsay 2003).

Unit of analysis issues

For cluster randomised trials, we plan to conduct the analysis at the same level as the allocation using a summary measure from each cluster. However, if this appears to unnecessarily reduce the power of the study due to the number and size of the clusters, we will seek statistical advice to determine if a risk ratio or standardised mean difference with confidence intervals can be calculated to account for the cluster design based on a 'multilevel model' or another appropriate method.

Dealing with missing data

If important data are missing, we will contact authors to attempt to obtain the data. We will use intention-to-treat analyses by including all participants that were supposed to have received a particular intervention. If necessary, we will also perform sensitivity analyses by excluding studies with high rates of loss to follow-up.

Assessment of heterogeneity

We plan to assess statistical heterogeneity in each meta-analysis visually and using the I^2 and Chi^2 statistics, regarding heterogeneity as substantial if the I^2 statistic is greater than 60% or if there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and we will conduct formal tests for funnel plot asymmetry, using the metabias command in STATA. We will use the test proposed by Egger 1997, which can be implemented easily in STATA.

Data synthesis

We will undertake meta-analyses only where they are meaningful (i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense). A common way that trialists indicate when they have skewed data is by reporting medians and interquartile ranges. When we encounter this we will note that the data are skewed and consider the implication of this. Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. intervention A versus usual care and intervention B versus usual care) must be entered into the same meta-analysis, we will halve the control group to avoid double counting. If studies are homogeneous enough for pooling their results to be clinically meaningful, we will perform a meta-analysis using a random-effects model. We will perform the analysis using RevMan (Cochrane 2014) and produce forest plots for all analyses.

We will extract data in the included studies on costs per death averted as reported by the study authors, but we will not attempt to calculate these costs.

Summary of findings

We will summarise the findings of the main intervention comparison for the most important outcomes:

- perinatal mortality rate;
- stillbirth rate;
- neonatal mortality rate;
- mortality rate in children under five years of age;
- maternal mortality ratio.

We will present these in a 'Summary of findings' table to draw conclusions about the certainty of the evidence within the text of the review. Two review authors will independently assess the certainty of the evidence (high, moderate, low or very low) using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias). We will use the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the EPOC worksheets (EPOC 2017c), and using GRADEpro software (GRADEpro GDT 2015). We will resolve disagreements on certainty ratings by discussion, provide justification for decisions to down- or upgrade the ratings using footnotes in the table and make comments to aid readers' understanding of the review where necessary. We will use plain language statements to report these findings in the review. We will consider whether there is any additional outcome information that was not able to be incorporated into meta-analyses, note this in the comments and state if it supports or contradicts the information from the meta-analyses. If it is not possible to meta-analyse the data we will summarise the results in the text.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses:

1. type of country (low- versus middle- versus high-income, according to World Bank classification at the time of the study);
2. type of death review (verbal and social autopsy versus SEA versus confidential enquiry);
3. setting: facility-based versus community-based.

The following outcomes will be used in subgroup analysis:

1. perinatal mortality rate;
2. stillbirth rate;
3. neonatal mortality rate;
4. mortality rate in children under five years of age;
5. maternal mortality ratio.

Sensitivity analysis

We will perform sensitivity analysis defined a priori to assess the robustness of our conclusions and explore its impact on effect sizes. This will involve:

1. restricting the analysis to published studies;
2. restricting the analysis to studies with a low risk of bias (i.e. high-quality randomised trials).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE, Ovid

#	Searches	Results
1	(child mortality/ or fetal mortality/ or infant mortality/ or maternal mortality/ or perinatal mortality/) and (clinical audit/ or medical audit/)	348
2	(Pregnant Women/ or exp Child/) and ("cause of death"/ or Mortality/) and (clinical audit/ or medical audit/)	57
3	(Pregnancy Complications/mo or Stillbirth/ or Suddent Infant Death/) and (clinical audit/ or medical audit/)	85
4	((maternal or mother* or maternity or child* or infan* or p?ediatric* or fetal or foetal or perinatal or pregnan* or childbirth or birth or labo?r) adj3 (mortality or death?)).ti,ab. and (clinical audit/ or medical audit/)	438
5	(stillbirth? or sudden infant death? or sids or cot death? or crib death?).ti,ab. and (clinical audit/ or medical audit/)	62
6	(child mortality/ or fetal mortality/ or infant mortality/ or maternal mortality/ or perinatal mortality/) and (review* or audit* or meeting? or enquir* or inquir*).ti,ab	4594
7	(Pregnant Women/ or exp Child/) and ("cause of death"/ or Mortality/) and (review* or audit* or meeting? or enquir* or inquir*).ti,ab	1732
8	(Pregnancy Complications/mo or Stillbirth/ or Suddent Infant Death/) and (review* or audit* or meeting? or enquir* or inquir*).ti,ab	1034
9	(((death? or mortality) adj3 (review* or audit* or meeting? or enquir* or inquir*)) and (maternal or mother* or maternity or child* or infan* or p?ediatric* or fetal or foetal or perinatal or pregnan* or childbirth or birth or labo?r)).ti,ab	2169
10	((stillbirth? or sudden infant death? or sids or cot death? or crib death?) adj5 (review* or audit* or meeting? or enquir* or inquir*)).ti,ab	346
11	((confidential enquir* or confidential inquir*) and ((maternal or mother* or maternity or child* or infan* or p?ediatric* or	341

(*Continued*)

	fetal or foetal or perinatal or pregnan* or childbirth or birth or labo?r) adj3 (mortality or death?))).ti,ab	
12	((confidential enquir* or confidential inquir*) and (stillbirth? or sudden infant death? or sids or cot death? or crib death?)).ti,ab	61
13	(cemach or cmace or cemd or cmde).ti,ab.	66
14	(saving mothers lives or making pregnancy safer or making childbirth safer).ti,ab	45
15	((verbal autops* or social autops*) adj5 (maternal or mother* or maternity or child* or infan* or p?ediatric* or fetal or foetal or perinatal or pregnan* or childbirth or birth or labo?r)).ti,ab	118
16	((near miss* or significant event* or critical event* or critical incident?) and (maternal or mother* or maternity or child* or infan* or p?ediatric* or fetal or foetal or perinatal or pregnan* or childbirth or birth or labo?r) and (review* or audit* or meeting? or enquir* or inquir*)).ti,ab	374
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	8610
18	exp Animals/ not humans/	4743197
19	17 not 18	8579
20	randomized controlled trial.pt.	505457
21	controlled clinical trial.pt.	100426
22	multicenter study.pt.	254745
23	pragmatic clinical trial.pt.	762
24	non-randomized controlled trials as topic/	266
25	interrupted time series analysis/	387
26	controlled before-after studies/	313
27	(randomis* or randomiz* or randomly).ti,ab.	820831
28	groups.ab.	1884241

(*Continued*)

29	(trial or multicenter or multi center or multicentre or multi centre).ti	234468
30	(intervention? or effect? or impact? or controlled or control group? or (before adj5 after) or (pre adj5 post) or ((pretest or pre test) and (posttest or post test)) or quasiexperiment* or quasi experiment* or pseudo experiment* or pseudoexperiment* or evaluat* or time series or time point? or time trend? or repeated measur* or step* wedg*).ti,ab	8860150
31	exp "Costs and Cost Analysis"/	224968
32	economics/ or exp economics, hospital/ or exp economics, medical/	64522
33	"Value of Life"/	5842
34	quality-adjusted life years/	10860
35	Decision Trees/	10839
36	economic evaluation*.ti,ab.	10364
37	(Cost* adj2 (Effective* or analysis* or Utility* or Benefit* or Minimi*)).ti,ab	145738
38	(pharmacoeconomic* or pharmaco-economic*).ti,ab.	4036
39	economic*.ti.	42813
40	("Value of life" or "quality adjusted life year*" or qaly* or qald* or qale* or "disability adjusted life year*" or daly).ti,ab	15327
41	(sf6 or short form 6 or shortform6 or euroqol or euro quality of life or eq5d or eq-5d).ti,ab	9979
42	(hye or health* year equivalent*).ti,ab.	62
43	(health utilit* or disutilit*).ti,ab.	2170
44	"willingness to pay".ti,ab.	4341
45	standard gamble.ti,ab.	867
46	(time trade off or time tradeoff or tto).ti,ab.	1748
47	(vas or visual analog*).ti,ab.	69360

(*Continued*)

48	((economic adj2 model*) or markov or monte carlo method).ti,ab	24887
49	(decision* adj (tree* or model* or analysis)).ti,ab.	12985
50	(resource* adj (use* or utilisation)).ti,ab.	9810
51	((healthcare or health care or direct service or hospital or drug*) adj cost*).ti,ab	31583
52	or/20-51	10160587
53	review.pt.	2480561
54	meta analysis.pt.	94844
55	news.pt.	190065
56	comment.pt.	734842
57	editorial.pt.	470195
58	cochrane database of systematic reviews.jn.	14591
59	comment on.cm.	734840
60	(systematic review or literature review).ti.	112324
61	or/53-60	3760993
62	52 not 61	9136353
63	19 and 62	2910

CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: all authors

Designing the protocol: MW, BN, JP, BS, AD, AH

Coordinating the protocol: MW

Designing search strategies: MW, NR

Writing the protocol: MW, BN, JP, BS

Providing general advice on the protocol: AH, AD

Performing previous work that was the foundation of the current study: AD, MW, BN, AH, HA, VM

DECLARATIONS OF INTEREST

Merlin L Willcox: no known conflicts of interest

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Jessica Price: no known conflicts of interest

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