Searching NHS EED and HEED to inform development of economic commentary for Cochrane intervention reviews

STUDY REPORT

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Executive Summary

E1. Background

It has been proposed that Cochrane Review Groups could consider encouraging authors of selected intervention reviews to conduct supplementary electronic searches of the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) in order to locate studies to inform development of brief, economic commentaries for inclusion in 'Background' and/or 'Discussion' sections of reviews. The aim is to increase the relevance and usefulness of Cochrane intervention reviews for end users through incorporation of economic perspectives and evidence, without major additional resource or workload implications for author teams or editorial bases.

E2. Study objective

To develop and evaluate methods processes for use to incorporate electronic searches of NHS EED and HEED into Cochrane intervention reviews and to use the results of these searches to inform development of brief economic commentaries.

E3. Methods

A retrospective pilot study using new Cochrane intervention reviews published in Issue 1, 2011 of the *Cochrane Database of Systematic Reviews*. Methods processes were developed and applied iteratively based on the study protocol. Key dimensions of process and search results were recorded and analysed.

E4. Recommended process for Cocharane intervention reviews

Based on the findings of this study, a recommended *minimum* process comprises the following stages:

- Develop two separate search strategies for each of NHS EED and HEED (i.e. two pairs, four in total), adapted from search strategies designed to locate studies of effects. The first is designed to capture NHS EED or HEED records of relevant full and partial economic evaluations ('economic evaluations'). The second is designed to capture NHS EED or HEED records of economic analyses that report information regarding economic burden/cost-of-illness of the health condition ('economic analyses')[1].
- Apply search strategies in NHS EED and HEED.
- Initial screening of retrieved NHS EED and HEED record sets to identify potentially eligible economic evaluations and economic analyses.
- Second round of screening of NHS EED and HEED record sets and (if required) corresponding article abstracts/full-texts. Screening of economic evaluations aims to confirm eligibility and to classify eligible economic evaluations by analysis type and

[1] Distinctions between the terms 'relevant full and partial economic evaluations' and 'economic analyses that report information regarding economic burden/cost-of-illness of the health condition' are fully explained in 'Methods, Section ##' on pp. ##.

framework. Screening of economic analyses aims to select the few economic analyses judged most useful to inform economic commentary focused on economic burden/ cost-of-illness of health condition.

- Use NHS EED and HEED records and corresponding article abstracts/full-texts of *selected* economic analyses to develop commentary focused on economic burden/ cost-of-illness of health condition. Integrate commentary into 'Background' section.
- Use NHS EED and HEED records and corresponding article abstracts/full-texts of *all* eligible economic evaluations to develop commentary on the *prima facie* case that an intervention might be judged favourably (or unfavourably) from an economic point of view. Integrate commentary into 'Discussion' section.
- Include bibliographic details of all economic analyses/ economic evaluations cited in the economic commentary in 'Additional references'.

E4. Results

Principal results of the analysis of key dimensions of process and search results were:

- At least one eligible economic evaluation was identified for 28% of included intervention reviews (10 of 36).
- The number of eligible economic evaluations was, on average (mean), 1.4 per included review for NHS EED and HEED combined (N= 36; Mean = 1.4, s.d.= 4.4; Range = 0 to 24).
- At least one potentially eligible economic analysis was identified for 70% of included reviews (21 of 30).
- The number of eligible economic analyses was, on average (mean), 23 per review selected for development of economic commentary (N= 5; Mean = 23.6, s.d.= 24.9; Range = 0 to 66).
- The aggregate trained researcher time input (time on task) required to complete all the processes undertaken in this study (selected reviews only) - including development and application of search strategies, screening and selection, classification of eligible economic evaluations and development of the economic commentary - was, on average (median), 3hours, 30 minutes per review (N=5; Median = 210 minutes; Mean = 245.6, s.d. = 140.3; Range = 93.0 to 450.0).
- If all recommendations of this study were implemented (inc. independent screening and classification of economic evaluations by two researchers), we estimate that the aggregate researcher time input (time on task) may increase, on average, to around 4 to 4.5 hours per review. Researcher time input (time on task) is likely to vary

considerably between reviews, contingent on a range of factors summarised and discussed in the main body of this report.

E5. Detailed recommendations

Based on the findings of this study, our overall conclusion is that the proposal described in E1 (above) is viable. We make 25 further provisional recommendations for consideration by the Editor-in-Chief of *The Cochrane Library* and Coordinating Editors of Cochrane Review Groups. These are summarised below[2]:

Recommendation 1: NHS EED and HEED search strategies aiming to locate the few most useful economic analyses that report information on the economic burden/ cost-of-illness of the health condition being addressed ('economic analyses') should use keyword search terms designed to capture 'Population' concepts. These search strategies can be adapted from 'Population' keyword search terms used in search strategies to identify relevant studies of effects.

Recommendation 2: NHS EED and HEED search strategies aiming to locate relevant full and partial economic evaluations ('economic evaluations', i.e. those that both compare the experimental intervention(s) and eligible comparator(s) studied in the intervention review and that meet eligibility criteria set with respect to population(s)) should use at least keyword search terms designed to capture 'Intervention' concepts. These search strategies can be adapted from 'Intervention' keyword search terms used in search strategies to identify relevant studies of effects.

Recommendation 3: Searches of NHS EED and HEED aiming to locate economic analyses should aim to identify the few analyses likely to be most useful to inform related economic commentary. In general, these are: recently conducted applied cost-of-illness studies or reviews of applied cost-of-illness studies that focus on international comparisons and that include estimates of societal burden/cost alongside burden/cost to health care systems.

Recommendation 4: Searches of NHS EED and HEED aiming to locate relevant economic evaluations should be sufficiently sensitive to locate *all* available, relevant published economic evaluations.

Recommendation 5: Authors should conduct searches of both NHS EED and HEED for the purpose of identifying *all* relevant published economic evaluations.

Recommendation 6: At present, authors should conduct searches of both NHS EED and HEED for the purpose of identifying the most useful and relevant economic analyses.

Recommendation 7: Once NHS EED no longer includes records other than structured abstract records (and provisional abstract records) of full economic evaluations (i.e.

[2] For further details and related discussion see 'Discussion and Recommendations' section of the main body of this report.

from 2012), authors should conduct searches of HEED only for the purpose of identifying the most useful and relevant economic analyses.

Recommendation 8: Where available, authors should retrieve and refer to abstracts and/or full-texts of corresponding articles to complete assessments of eligibility (and classification, in the case of economic evaluations), if information contained in the NHS EED and/or HEED record proves insufficient for this purpose.

Recommendation 9: Screening NHS EED and HEED records and corresponding article abstracts and/or full-texts (if required) to assess the eligibility of economic evaluations and to classify the type of analysis and framework used should be completed independently by two researchers, with resolution of any disagreements through discussion.

Recommendation 10: Assessment of the eligibility of economic evaluations should be based on those eligibility criteria set for the corresponding intervention review that relate to Population(s), Interventions(s) and Comparison(s).

Recommendation 11: In addition to a clear understanding of relevant eligibility criteria set for the corresponding intervention review to inform assessments of eligibility of economic evaluations, classification type of analysis and framework used can be assisted by an established classification scheme for types of economic evaluation (analysis type) and descriptions of the main types of full economic evaluation published in Chapter 15 of the *Cochrane Handbook for Systematic Reviews of Interventions*.

Recommendation 12: Screening the results of NHS EED and HEED searches aiming to locate economic analyses should focus primarily on confirming the relevance of each record/analysis to the health condition of interest and also that it is a good candidate (see Recommendation 3) to inform development of related economic commentary. It is not judged necessary that screening of the results of these searches should be completed independently by two researchers.

Recommendation 13: Where available, authors should draw on the contents of NHS EED structured abstract records and/or HEED field-coded abstract records to inform the development of economic commentaries.

Recommendation 14: Where available, authors should additionally draw on corresponding full-text articles to inform the development of economic commentaries. Use of corresponding full-text articles alongside NHS EED structured abstract records and/or HEED field-coded abstract records serves two purposes: identifying useful supplementary information that is not included in the NHS EED or HEED record; and resolving any discrepancies between NHS EED or HEED records (if both are available). If NHS EED and/or HEED records are (both) citation only records, corresponding abstracts and/or full-text articles will be the primary source for development of economic commentaries.

Recommendation 15: In line with other sources cited in the 'Background' section of a review, it is not necessary to subject those economic analyses selected as sources to inform development of economic commentary regarding economic burden/ cost-of-illness of the health condition to formal critical appraisal.

Recommendation 16: Authors of reviews will need to decide whether to subject economic evaluations used as sources to inform development of economic commentary regarding the *prima facie* case that an intervention might be judged favourably (or unfavourably) from an economic point of view to formal critical appraisal. This decision is likely to depend on the number of economic evaluations to be appraised, the time available to be allocated to the overall process of developing economic commentaries, and the availability of health economics expertise within the author team.

Recommendation 17: If authors of reviews decide not to subject source economic evaluations to formal critical appraisal, they should include an explicit statement of this fact in the related economic commentary.

Recommendation 18: If authors decide to subject source economic evaluations to formal critical appraisal, a recognised checklist should be used to inform this process (alongside 'critical commentary' sections of NHS EED structured abstract records, if available). The 'study limitations' component of a methodology checklist recommended for critical appraisal of economic evaluations by the National Institute for Health and Clinical Excellence may be used for this purpose (NICE 2009). Checklist(s) should be completed independently by two researchers, with resolution of any disagreements through discussion.

Recommendation 19: If authors decide to subject source economic evaluations to formal critical appraisal, they should include a brief summary of the main strengths and limitations of these evaluations in the economic commentary. The consensus judgements made by researchers in using the checklist (recorded in the comments section of the checklist), as well as 'critical commentary' sections of NHS EED structured abstract records (if available), can be used to inform development of this summary.

Recommendation 20: Economic commentary regarding economic burden/ cost-of-illness of the health condition *may* usefully include the following information (contingent on the scope of the most useful available source economic analyses): a brief, general statement of the scale of economic burden/ cost-of-illness to health care systems, patients and/or their families, and/or society as a whole; monetised estimate(s) of the scale of economic burden to health care systems; monetised estimate(s) of the scale of economic burden to patients and/or their families; monetised estimate(s) of the scale of economic burden to societies as a whole. Economic commentary regarding economic burden/ cost-of-illness of the health condition *should* include: details of currency and price year for any monetised estimates.

Recommendation21: Economic commentary focusing on the *prima facie* case that an intervention might be judged favourably (or unfavourably) from an economic point of view *should* include brief details of the: electronic health economics literature databases searched; number of relevant economic evaluations identified; primary types of analysis used in relevant economic evaluations (i.e. cost analysis; cost-effectiveness analysis; cost-utility analysis; cost-benefit analysis); frameworks used to assemble data for relevant economic evaluations (i.e. conducted within the framework of a randomised controlled trial; conducted using the framework of a decision model); analytic perspectives and time horizons adopted for costs and (if applicable) effects; main cost categories included in the analysis (e.g. hospital care costs, direct health care costs; indirect non-health care costs); currency and price year; principal conclusions made by authors of included economic evaluations (base case analysis); uncertainty regarding authors' principal conclusions based on any sensitivity analyses conducted. Such commentary should also include a brief description of any tentative inferences that can be drawn regarding the *prima facie* case that an intervention might be judged favourably (or unfavourably) from an economic point of view *and* appropriate caveats for any tentative inferences. If only one or two relevant economic evaluations are identified, commentary focusing on this issue *may* include principal results collected from each study that estimate the relative costs and/or relative efficiency of the alternatives compared (e.g. measures of incremental cost, incremental cost per unit of effect, or incremental cost per QALY intervention(s) versus comparator(s)). In this case, the commentary should also include details of the currency and price year applicable to all monetised estimates. Where several economic relevant economic evaluations are identified, it may not be judged feasible to summarise principal results collected from each study; instead it is recommended to focus solely on summarising authors' principal conclusions.

Recommendation22: Where economic commentary includes monetised estimates of economic burden/cost-of-illness, costs and/or relative efficiency collected from one or more published studies, conducted in different countries and/or at different times, authors may consider presenting estimates that are adjusted to a common target currency and price year, in order to facilitate comparison of estimates between studies. A free, web-based cost conversion tool that may be used for this purpose is available online at http://eppi.ioe.ac.uk/costconversion/default.aspx. This web-page includes a link to an article that includes guidance on use of the tool for this specific purpose (Shemilt 2010).

Recommendation23: All source published reports of economic analyses and/or economic evaluations that are used to inform development of economic commentary should, at minimum, be cited in 'Additional references'. With respect to published reports of source economic evaluations, authors may wish to consider providing a separate, annotated bibliography as an appendix to the review. If the latter option is chosen, annotation that could usefully supplement each citation would describe key

characteristics of source economic evaluations. At minimum, this should comprise the primary type of economic analysis and type of framework used (see also Recommendation 21). In addition, the annotation could usefully include the main cost categories included in the analysis (see Recommendation 21); the analytic perspectives and time horizons adopted for costs and (if applicable) effects.

Recommendation24: Cochrane intervention reviews that should be prioritised for encouraging author teams to develop an economic commentary are those that include comparison(s) of experimental intervention(s) with one or more alternative management strategies (i.e. not focused exclusively on comparison(s) between experimental intervention(s) and placebo) and in which important cost differences can be expected between the experimental intervention(s) and comparator(s) being considered, for at least of one three reasons: large difference in upfront costs of interventions; large difference in downstream costs of managing subsequent events (short or long-term); small cost difference (upfront costs and/or downstream costs) but large patient populations affected. Additionally, update reviews may be prioritised for development of economic commentaries over new reviews.

Recommendation 25: CRGs should consider seeking specialist peer review for economic commentaries of the form proposed in this study. If a CRG does not have access to specialist peer review from CRG-linked health economists, they should contact the Campbell and Cochrane Economics Methods Group.

Contents

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Tables and Figures

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1. Introduction

1.1. Background

Two electronic health economics literature databases freely available to contributors to The Cochrane Collaboration are the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED). NHS EED is available on the internet and is also published as part of *The Cochrane Library*. It contains over 7,000 structured critical abstracts of published reports of full economic evaluations (i.e. cost-effectiveness analyses, cost-utility analyses and cost-benefit analyses), including expert commentary ('structured abstract records'), and also (at present) over 17,000 'citation only records' that provide bibliographic details of, *inter alia*, partial economic evaluations (i.e. cost analyses, cost descriptions and cost-outcome descriptions), cost-of-illness studies, and reviews of all those types of health economic analyses listed above.

HEED is marketed independently by Wiley Interscience as a subscription only database. Since January 2011 it has been made accessible, free at the point of use, to all contributors to The Cochrane Collaboration with an Archie user account via the cochrane.org intranet. It includes over 30,000 field-coded abstracts, without critical commentary ('field-coded abstract records'), and over 13,000 other records that provide bibliographic details ('citation only records'), of published reports of all those types of health economic analyses listed above.

It has been proposed by the Editor-in-Chief of *The Cochrane Library*, in consultation with the Campbell and Cochrane Economics Methods Group (CCEMG), that Cochrane Review Groups (CRGs) could consider encouraging authors of selected Cochrane intervention reviews to conduct supplementary electronic searches of NHS EED and HEED. The results of these searches would be processed alongside electronic searches of other literature databases, whether or not the review includes an explicit objective to incorporate evidence for resource use, costs and/or cost-effectiveness[3] alongside evidence for health (and related) outcomes. The main purposes would be to identify NHS EED and HEED records of all relevant economic evaluations and selected other potentially useful economic analyses, to flag the former to potential users of the review, and to use the content of these records (possibly in conjunction with abstracts and/or

[3] This explicit objective may be expressed in a protocol in terms of one or more of the following: specification of a (secondary) objective to critically appraise and summarise current evidence for resource use, costs and/or cost-effectiveness; specification of types/forms of health economic analysis amongst types of studies to be considered in the review; specification of measures of resource use, costs and/or cost-effectiveness amongst types of outcomes to be considered in the review (the latter three options are concerned with developing the review question and developing criteria for including studies); specification of economics methods for use in searching for studies, selecting studies and collecting data, assessing risk of bias in included studies, analysing data and undertaking meta-analysis, addressing reporting biases, presenting results and 'Summary of findings' tables and/or interpreting results and drawing conclusions.

full-texts of the published reports) to inform development of 'economic commentary' to be included in the 'Background' and/or 'Discussion' sections of the review. The overarching aim of this proposal is to increase the relevance and usefulness of Cochrane intervention reviews for end users who look to such reviews to help inform decisions that increasingly need to take account of economic issues, but without major additional resource or workload implications for author teams or editorial base staff.

This proposal is compatible with current guidelines on the use of economics methods in the preparation of Cochrane intervention reviews (Shemilt 2008). It can be expressed in terms of the first two of three potential roles served by incorporating economics perspectives and evidence in such reviews, which build (incrementally) on electronic searches of NHS EED and/or HEED (alongside electronic searches of other literature databases):

> R1. Include a bibliography of identified published reports of relevant health economic analyses as an appendix to the review (possibly annotated with selected characteristics of studies);
>
> R2. Develop 'economic commentary' to be included in the 'Background' and/or 'Discussion' sections of the review (inc. listing cited studies in 'Additional references');

For example, the 'Background' sub-section that describes the health condition addressed by the experimental intervention(s) being reviewed (i.e. 'Description of the condition') could include information about the economic burden and cost-of-illness of that condition. Similarly, there may be a case for including information regarding the *prima facie* case that an intervention might be judged favourably (or unfavourably) from an economic point of view in the 'Discussion' section, based on the findings of relevant full and partial economic evaluations; and

> R3. Full incorporation of evidence for resource use, costs and/or cost-effectiveness into the review[4], alongside evidence for health and related outcomes.

1.2. Study objectives

The principal objective of this study was to develop and evaluate methods processes for use to incorporate electronic searches of NHS EED and HEED into Cochrane intervention reviews and to use the results of these searches for the purposes described in R1 and R2, above ('Introduction', Section 1.1).

[4] Stages of research (review process) indicated by each of the three roles builds (stepwise) on those indicated by the preceding option, such that a review may, in principle, reflect 'Role 1 only', 'Roles 1 and 2', or 'Roles 1, 2 and 3'. However, the Editor in Chief's proposal is that, regardless of whether or not authors intend to proceed to stages of research indicated by Role 3, they could be encouraged to conduct electronic searches of NHS EED and HEED and to process the results of these searches in order to complete those stages of research indicated by Roles 1 and 2.

To address this principal objective, the proposed study aimed to address the following sets of questions:

Q1. How many relevant NHS EED and HEED records would have been retrieved if Cochrane intervention reviews had incorporated searches of these databases and what types of published health economic analyses (study design – analysis type) do these records describe? What is the unique yield and level of duplication between relevant records retrieved from NHS EED and HEED respectively?

Q2.How can the content of relevant NHS EED and HEED records be used by authors of Cochrane reviews (i.e. without further input from a health economist) to develop economic commentary to be included in the background and/or discussion sections of the review?

Q3. To what extent are NHS EED and HEED records alone sufficient to develop economic commentary (i.e. to what extent might authors also need to retrieve and draw on abstracts and/or full texts of published reports of the health economic analyses)?

Q4. What distinct information that may usefully be included in an economic commentary' is sourced from NHS EED and HEED records respectively (and/or corresponding abstracts or full-texts of published reports)?

Q5. What (if any) are the differences or inconsistencies between NHS EED and HEED in terms of the records of economic evaluations/economic analyses they contain and/or the information in the respective records, and how might authors resolve any inconsistencies?

Q6. What are the strengths and limitations of economic commentaries based on NHS EED and HEED records (and/or abstracts and/or full-text reports) that have not been subjected to the full systematic review process (e.g. assessments of: risk of bias, study limitations, heterogeneity and generalisability; adjustment of cost data)? What are the limits and recommended forms of 'evidence statement' (i.e. inferences drawn on the basis of NHS EED and HEED records and/or abstracts and/or full texts of published reports) that can be included in such commentaries? How should these issues be evaluated and reflected in guidelines and training materials for authors on developing such commentaries?

Q7. What criteria may be used to prioritise reviews in which it is likely to add most value to incorporate searches of NHS EED and HEED for the purposes described in R1 and R2 above?

Q8. How much additional research time is likely to be required to design and run searches of NHS EED and HEED and to use the contents of database records

(and/or abstracts/ full texts of corresponding published reports) to develop an economic commentary?

This study was conducted between January and March 2011 by Ian Shemilt (IS) on behalf of the Campbell and Cochrane Economics Methods Group (CCEMG). It was commissioned by David Tovey, Editor-in-Chief of *The Cochrane Library*, with funding support provided by the Cochrane Editorial Unit.

2. Methods

2.1. Sample

Full-text copies of all new Cochrane intervention reviews published in Issue 1, 2011 of the *Cochrane Database of Systematic Reviews* were retrieved from *The Cochrane Library* (www.thecochranelibrary.com) on 24 January 2011. Each review was allocated to one of two groups: those that already included searches of NHS EED or HEED (Group A) and those that did not (Group B)[5].

2.2. Search strategies

For each Group B review, subject search terms reproduced in the published review were adapted to configure two sets of search strategies for each of NHS EED and HEED:

- Search strategies designed to capture records of relevant full and partial economic evaluations[6];
- Search strategies designed to capture records of economic analyses containing relevant and potentially useful information on the economic burden and/or cost-of-illness of the health condition addressed by the experimental intervention(s) (and comparator intervention(s), if applicable).

For each review, the two search strategies were applied in NHS EED and HEED respectively between 24 January and 11 February 2011. Retrieved NHS EED and HEED record sets were subjected to initial screening ('Screen 1', based on the record title and NHS EED record and/or HEED record only) by one researcher (IS) to identify potentially relevant (and therefore potentially eligible) economic evaluations and potentially relevant and useful (and therefore potentially eligible) economic analyses.

[5] In practice, all retrieved reviews were allocated to Group B.

[6] Relevant full and partial economic evaluations are defined as those that both compare the experimental intervention(s) and eligible comparator(s) studied in the corresponding intervention review and that meet eligibility criteria set with respect to population(s). No restrictions were applied with respect to the framework for economic evaluation (i.e. empirical study or decision model) or the sources of data utilised (e.g. data for beneficial and adverse effects could be source from randomised or non-randomised studies, including a synthesis of such studies).

2.3. Initial screening

The potential eligibility of economic evaluations ('Screen 1') was assessed with reference to published information on 'Types of participants' and 'Types of interventions' extracted from the 'Criteria for considering studies for this review' sub-section of the 'Methods' section of the corresponding intervention review (supplemented with reference to any description of the experimental (and comparator) intervention(s) in the 'Background' section and/or to information on 'Comparisons' analysed in the 'Results' section)[7].

The potential eligibility of economic analyses was assessed with reference to information describing the health condition addressed by the experimental intervention (and comparator interventions, if applicable), extracted from the 'Background' section of the corresponding intervention review. Additional eligibility criteria applied to economic analyses were that they must report estimates of the economic burden/cost-of-illness of the health condition for *at least* a national-level; they must relate to the whole participant/patient group(s) of interest rather than to sub-groups of that population[8]; and they must be reported in a peer reviewed journal article.

Bibliographic details of articles reported in potentially eligible records were recorded. For each review, NHS EED and HEED record sets were compared to identify duplicate records[9] of potentially eligible economic evaluations and economic analyses. Counts of records of potentially eligible economic evaluations and economic analyses that were unique to NHS EED, unique to HEED, or duplicates were recorded. NHS EED and HEED records of potentially eligible economic evaluations and economic analyses went forward to a second round of screening.

2.4. Second round of screening and classification of eligible records/articles

The second round of screening ('Screen 2') was also conducted by one researcher (IS). This involved further assessment of record/article eligibility based on the abstract and/or full-text of the corresponding article (i.e. in addition to the NHS EED record and/or HEED record) – the abstract/full-text was referred to (if available) in the case that a potentially eligible record/article could not be confirmed as eligible (or excluded)

[7] Effectively, this means that potential eligibility was assessed based on 'Population(s)'. 'Intervention(s)' and 'Comparison(s)' components of the PICO eligibility criteria.

[8] Economic analyses based on local or regional data were excluded unless these data were extrapolated to estimate economic burden/ cost-of-illness for *at least* a national level. Occasional exceptions were made to this rule if the results of an analysis that did not meet these additional eligibility criteria provided insight into specific aspects of economic burden/ cost-of-illness of the health condition that had been identified as aspects of interest in the corresponding intervention review, but which were not covered in other analyses that fully met all eligibility criteria).

[9] Records of the same article available in both NHS EED and HEED.

with confidence based on the NHS EED record and/or HEED record alone[10]. For economic evaluations, this second round of screening ('Screen 2') was also conducted with more detailed reference to reference lists of included and excluded studies of effects published in the corresponding intervention review.

For economic analyses (economic burden/cost-of-illness), the second round of screening ('Screen 2') was applied *only* to potentially eligible records/articles of those reviews being considered as candidates for development of economic commentaries[11]. This pragmatic decision was made due to the large number of potentially eligible records that had been identified across all included intervention reviews following initial screening ('Screen 1'); it was not judged feasible to complete the more time intensive second round of screening for all of these records within the scope of this study (>1,000 HEED and NHS EED records, plus abstracts and/or full-texts if required).

Figure 1. Adapted classification scheme for different types of evaluation

Are both costs (inputs) and consequences (outputs) of the alternatives examined?

Is there comparison of two or more alternatives?	No		Yes
No	*Examines only consequences*	*Examines only costs*	
	1A Partial evaluation Outcome description	1B Cost description	2 Partial evaluation Cost-outcome description
Yes	3A Partial evaluation Efficacy or effectiveness evaluation	3B Cost analysis	4 Full economic evaluation Cost-effectiveness analysis (CEA) Cost-utility analysis (CUA) Cost-benefit analysis (CBA)

Counts of records of eligible economic evaluations/ economic analyses that were unique to NHS EED, unique to HEED, or duplicates were recorded. Eligible economic evaluations were then classified by analysis type using an adapted version of an

[10] The availability of abstract and/or full-text texts in local library resources was established for each potentially eligible economic evaluation (see Appendix 4, Table A4.1) , but these were only retrieved if either a potentially eligible record could not be confirmed as eligible (or excluded) with confidence based on the NHS EED record and/or HEED record alone, or if the corresponding intervention review was considered a candidate for development of an economic commentary.

[11] As for economic evaluations, the availability of abstract and/or full-text texts in local library resources was established for each potentially eligible economic analysis (see Appendix 4, Table A4.1) , but these were only retrieved if either a potentially eligible record could not be confirmed as eligible (or excluded) with confidence based on the NHS EED record and/or HEED record alone, or if the corresponding intervention review was considered a candidate for development of an economic commentary.

established classification scheme (Drummond 2005), reproduced in Figure 1 (above). Cost-consequences analyses were classified as a sub-set of cost-effectiveness analyses, in line with current Cochrane methods guidance and the convention used in NHS EED structured abstract records (Shemilt 2008, Craig 2007). Some NHS EED records classify an economic evaluation as both a cost-effectiveness analysis and a cost-utility analysis, or as both a cost-effectiveness analysis and a cost-benefit analysis[12]. In this study, such records were classified as cost-utility analyses or cost-benefit analyses[13] respectively, since this is regarded as the primary analysis type. Eligible full economic evaluations (i.e. cost-effectiveness analyses, cost-utility analyses and cost-benefit analyses[11]) were further classified according to whether they had been conducted within the framework of (or based upon) an empirical study (e.g. a randomised controlled trial or non-randomised study design) or using the framework of a decision model (e.g. simple decision tree, Markov chain, individual sampling). These classifications were undertaken concurrently with the second round of screening ('Screen 2') and with reference to the NHS EED and/or HEED record and/or article abstract and/or full-text, as required. Details of the classification process were recorded.

Eligible economic analyses (economic burden/ cost-of-illness) were classified as one of the following types[14]:

- Cost-of-illness analysis (applied study).
- Review of applied cost-of-illness analyses.
- Cost-of-illness analysis (applied study) conducted alongside cost-effectiveness analysis (cost-consequences).
- Cost-of-illness (applied study) conducted alongside an econometric analysis.

As with eligible economic evaluations, classifications were undertaken concurrently with the second round of screening ('Screen 2') and with reference to the NHS EED and/or HEED record and/or article abstract and/or full-text, as required. Details of the classification process were recorded.

[12] Strictly, such NHS EED records are accurate, since both a cost-utility analysis and a cost-benefit analysis build on all stages of research undertaken in a cost-effectiveness analysis by valuing effects in terms of (respectively) quality adjusted life years/ disability adjusted life years (cost-utility analysis) or their monetary value (cost-benefit analysis). However, NHS EED records are not entirely consistent in applying this 'dual-code' to all cost-utility analyses and cost-benefit analyses, and in any case the primary analysis is the cost-utility analysis or cost-benefit analysis.

[13] In practice, no cost benefit analyses were identified.

[14] This classification scheme was developed iteratively during the classification process and is exhaustive of those types of economic analysis (economic burden/ cost-of-illness) encountered during this study.

2.5. Economic commentaries

A purposive sample of five included intervention reviews was selected for development of economic commentaries. Reviews considered for selection were those for which at least one relevant economic evaluation had been identified as eligible following the second round of screening ('Screen 2'). Other selection criteria were that each selected review should fall under the editorial responsibility of a different Cochrane Review Group (to ensure coverage of a range of health conditions) and that the experimental intervention(s) studied across the five selected reviews should include at least one surgical intervention and at least one pharmaceutical intervention. Selection was also made based on the subjective judgement of the researcher (IS) that selected reviews would be likely to elucidate a range of issues relevant to the development of recommendations and subsequent guidance on methods processes that may be used to develop economic commentaries for inclusion in Cochrane intervention reviews.

For each selected review, an economic commentary was developed and integrated into 'Background' and/or 'Discussion' sections of the published review. In the first instance, development of economic commentary was informed solely by eligible NHS EED and/or HEED records. Subsequently, further development of commentary in each review drew on any additional useful information that was only available in article abstracts and/or full texts. The source(s) of information used in each economic commentary were recorded (see Results, Section 3.4.2).

2.6. Assessment of yields of eligible records from original searches of general electronic biomedical databases

Search strategies applied in Medline, Embase and/or the Cochrane Central Register of Controlled Trials (Central) to locate eligible studies of effects in each intervention review were re-run to assess the extent to which these original search strategies would also have captured eligible economic evaluations (original search strategies re-run for ten intervention reviews for which one or more eligible economic evaluations had been identified) and eligible economic analyses (economic burden/ cost-of-illness – original search strategies re-run for five intervention selected for development of economic commentary). Original search strategies could only be re-run for a review if the published review both: (i) indicated that the authors had conducted a search of Medline, Embase and/or Central to locate eligible studies of effects; (ii) provided sufficient details of original search strategies to allow these to be replicated. Original Medline and Embase search strategies were re-run both with and without search filters designed to restrict records to randomised controlled trials (if applicable).

2.7. Assessment of study limitations: eligible economic evaluations

Once economic commentaries had been completed and integrated into the corresponding intervention review, each eligible economic evaluation was subjected to critical appraisal (assessment of study limitations) based on application of a recognised checklist for economic evaluations (NICE 2009). The time taken to complete this checklist for each eligible economic evaluation was recorded. Each economic commentary then was reassessed with reference to corresponding completed checklists. Implications for each 'economic commentary', in terms of edits indicated based on the critical appraisal, were recorded.

2.8. Researcher time input

The time taken (time on task) to complete each of the research processes described in 'Methods', Sections 2.2-2.5 and 2.7 (above) was recorded.

2.9. Analysis and presentation of results

All process data and search results described in 'Methods' Sections 2.2-2.8 (above) were recorded and stored in Word or Excel files. Quantitative data were analysed using SPSS to generate descriptive statistics. All results are presented in the form of a narrative summary, supplemented by additional tables.

3. Results

3.1. Retrieved reviews

Thirty-eight new intervention reviews were published in Issue 1, 2011 of the *Cochrane Database of Systematic Reviews* (see Appendix 1). None of the reviews already included searches of NHS EED or HEED. The reviews span a range of health care topics and collectively fall under the editorial responsibility of 25 Cochrane Review Groups. Two reviews did not publish electronic search strategies designed to locate relevant studies of effects, and were therefore excluded from this study (Eke 2011, Abdel-Aleem 2011).

3.2. Searches for relevant economic evaluations

3.2.1. Formulating search strategies

The process of formulating NHS EED and HEED search strategies designed to capture records of relevant full and partial economic evaluations was completed, on average (median), in 14 minutes (N= 36; Median = 13.5; Range = 3 to 35; Mean = 13.7; s.d.= 7.6). Final NHS EED and HEED search strategies executed in this study are reproduced in Appendix 2. Searches of NHS EED were configured to run in the search interface located on the main database web-page (which, by default searches all text in the record title, text and keywords). In most cases, searches of HEED were configured using the 'Expert search' interface.

In many cases, NHS EED and HEED search strategies for economic evaluations utilised only search terms designed to capture 'Intervention' (and in some cases 'Comparison') concepts. This was a pragmatic decision made for two reasons. First, search terms designed to capture 'Intervention' (and 'Comparison') concepts are more sensitive than those that combine the latter with search terms designed to capture 'Population' concepts[15] but the record sets retrieved were judged manageable[16] in terms of the numbers of records and time available to be allocated to the screening process. Second, current NHS EED and HEED search interfaces are somewhat limited compared with those of general electronic biomedical literature databases such as Ovid Medline and Ovid Embase, in terms of the length and complexity of search strategies that can be executed successfully - in many cases (dependent of numbers of search terms used in the source intervention review), combining search terms designed to capture 'Intervention' (and 'Comparison') concepts with those designed to capture 'Population' concepts is simply not feasible. In the few cases that record sets retrieved using search strategies that utilise only search terms designed to capture 'Intervention' (and

[15] Inclusion of search terms that capture 'Study design' and/or 'Outcomes' concepts is inappropriate for the purpose of conducting electronic searches designed to locate economic evaluations in these specialist tertiary databases.

[16] Manageable within the scope of this study.

'Comparison') concepts were not judged manageable, combining the latter with search terms for 'Population' concepts (if feasible) and/or (in HEED) relevant ICD-9 Codes (effectively, these perform the same function as search terms for 'Population' concepts) proved a successful strategy to reduce record sets to manageable sizes, without compromising sensitivity.

Invariably, search strategies needed to be adapted for NHS EED and HEED from those used in electronic searches for studies of effects in the source review, in order to allow them to be executed successfully in the NHS EED and HEED search interfaces. First, a pragmatic decision was taken to limit these NHS EED and HEED searches to keyword searches of all record text (i.e. MeSH terms were excluded). In our experience, combining keyword searches with MeSH term searches in NHS EED is problematic. Second, NHS EED and HEED do not handle replications of keywords within search strings as easily as general electronic biomedical literature databases such as Ovid Medline and Ovid Embase, with the result that search strategies which include such replications fail to execute successfully. Almost all adaptations made in the process of formulating search strategies for NHS EED and HEED had the effect of increasing sensitivity, which consequently increased the size of the record sets retrieved. For all the reasons outlined above, more than one iteration of each strategy was tested before a strategy was identified that could execute successfully in each database.

In most cases, final versions of NHS EED search strategies for economic evaluations were very similar to those executed in HEED, but rarely identical. Frequent minor differences were necessary due to differences between the respective search interfaces, such as the more limited range of Boolean operators available in HEED (e.g. NHS EED allows use of the operator 'NEAR', whilst HEED does not, such that the operator 'AND' must be used instead).

3.2.2. Processing search results: 'Screen 1' (NHS EED and HEED records only)

On average (mean), the total number of records retrieved by searches for relevant economic evaluations was 25 per review for NHS EED (N= 36; Mean = 25.1, s.d.= 41.7; Range = 0 to 213) and 32 per review for HEED (N= 36; Mean = 31.5, s.d.= 65.4; Range = 0 to 371). Following initial screening of records sets for each database (i.e. screening based on the NHS EED or HEED record only), one or more potentially eligible records were identified for 31% of reviews (11 of 36).

Amongst those reviews with one or more potentially eligible records, the average (mean) number of records that passed initial screening was 4 per review for NHS EED (N= 11; Mean = 4.4, s.d.= 6.2; Range = 1 to 22) and 6 per review for HEED (N= 9; Mean = 6.2, s.d.= 8.7; Range = 1 to 28). On average (mean), with respect to potentially eligible

records this equates to a Number-Needed-to-Read[17] of 17 per review for NHS EED (N= 11; Mean = 17.4, s.d.= 25.0; Range = 1 to 68) and 13 per review for HEED (N= 9; Mean = 13.3, s.d.= 20.3; Range = 1 to 66).

Amongst those reviews with one or more potentially eligible records, accounting for duplicate records the average (mean) total number of potentially eligible articles was 6 per review for NHS EED and HEED combined (N= 11; Mean = 6.3, s.d.= 9.2; Range = 1 to 32). Full details of unique and duplicate yields of potentially eligible records between NHS EED and HEED by review, are provided in Appendix 3, Table A3.1. Average (mean) total numbers of records unique to NHS EED, records unique to HEED and duplicate records (potentially eligible records) were: 1 per review (N= 11; Mean = 1.1, s.d.= 0.9; Range = 0 to 3), 2 per review (N= 11; Mean = 1.8, s.d.= 2.8; Range = 0 to 9) and 3 per review (N= 11; Mean = 3.3, s.d.= 5.6; Range = 0 to 19) respectively.

On average (median), initial screening of records sets retrieved from both databases was completed in a total time of 5 minutes per review (N= 36; Median = 5.0; Mean = 18.4 s.d.= 51.1; Range = 0 to 301). Time taken to complete this process was (unsurprisingly) correlated with the size of retrieved records sets (N = 36; Pearson correlation co-efficient = 0.96; $p<0.001$). The average (median) time taken to screen a single NHS EED or HEED record ('Screen 1') was approximately 20 seconds (N= 34; Median = 0.3 mins; Mean = 0.4 mins, s.d.= 0.3; Range = 0.07 to 1.35 mins).

3.2.3. Processing search results: 'Screen 2' (Assessment of eligibility based on article abstracts and/or full-texts and classification of eligible records/articles by type of economic evaluation)

Following the second stage of screening (i.e. assessment of eligibility based on the abstract and/or full-text of the corresponding article), the number of eligible articles[18] was, on average (mean), 1.4 per review for NHS EED and HEED combined (N= 36; Mean = 1.4, s.d.= 4.4; Range = 0 to 24), with one or more eligible records/articles of economic evaluations identified for 28% of reviews (10 of 36).

Classification of eligible records/articles by type of economic evaluation revealed that, across all included reviews, the most frequently eligible type of economic evaluation was a cost-utility analysis conducted using the framework of a decision model (25%, 13 of 51), followed by a cost effectiveness analysis conducted using the framework of a decision model (24%, 12 of 51) and a cost effectiveness analysis conducted within the

[17] In the context of this study, Number-Needed-to-Read is defined as an index of how many records (and articles) have to be read to find one of adequate relevance or potential usefulness.

[18] As well as records/articles whose eligibility could be established with confidence, figures for 'eligible records/articles' includes any potentially eligible records/articles that could not be excluded with confidence following this second round of screening, because the NHS EED and/or HEED record was 'citation only' and either the abstract nor full-text of the corresponding article could be retrieved, or only the abstract could be retrieved and the record/article still could not be excluded with confidence.

framework of an empirical study (16%, 8 of 51). No records/articles reporting cost-benefit analyses were identified. The full classification of eligible records/articles by type of economic evaluation and framework is provided in Appendix 3, Table A3.3. These figures do not exclude articles reporting economic evaluations that are in some sense non-independent (e.g. where multiple articles report economic evaluations that appear, to different degrees, to utilise the same (or overlapping) source(s) of data of different types)[19].

The processes of assessing the eligibility of records/articles with reference to eligibility criteria set for the corresponding intervention review, and their classification by type of economic evaluation and framework, *required* retrieval and examination of the article abstract and/or full-text (i.e. could not be completed with confidence based on the NHS EED and/or HEED record alone) in 24% of cases (12 of 51) – see also Appendix 3, Table A3.4. Examination of the corresponding abstract and/or full text article was invariably required for these purposes in cases that the NHS EED and/or HEED record was a citation only record (i.e. did not include information other than bibliographic details of the corresponding article)[20].

However, retrieval and examination of the article abstract and/or full-text was also required in cases that: (i) insufficient detail was available about the population, experimental intervention(s) and/or comparator(s) in the NHS EED and/or HEED record to allow confident assessment of eligibility; or (ii) the record's classification of analysis type appeared potentially incorrect, misleading or confusing. The latter issue (ii) was encountered relatively infrequently in this study with respect to full economic evaluations (i.e. NHS EED structured abstract records and HEED field-coded abstract records appear, in general, to provide reliable classifications of full economic evaluations)[21]. However it was encountered more frequently in HEED field-coded abstract records with respect to economic evaluations classified in this study as cost analyses, but which were sometimes not classified as cost analyses in the HEED record. It was also encountered in HEED records with respect to records that were classified in this study as reviews of applied cost-of-illness studies, in which case the 'Type of Economic Evaluation' field sometimes (potentially misleadingly) includes additional codes for the types of economic evaluation identified in the review of applied studies

[19] Development of a comprehensive 'map' of the relationships between eligible economic evaluations and the sources of data they utilise, by review, was beyond the scope of this study, but it is important to consider such issues of 'non-independence' if the aim is to conduct a systematic review of such studies or to develop economic commentary based on eligible economic evaluations.

[20] In NHS EED, this currently applies to records of all types except for structured abstract records of full economic evaluations (i.e. cost-effectiveness analyses, including cost consequences analyses; cost-utility analyses; and cost-benefit analyses), including provisional abstract records (i.e. records of full economic evaluations for which a structured abstract record has not yet been produced, but is either scheduled to be produced or may be produced on request.

[21] Mislabelling of economic evaluations by analysis type has been identified as an issue in previous empirical studies that have warned against 'judging economic studies by their label', due to variations in conventions for classifying/ reporting 'analysis type' across settings (e.g. Zarnke 1997).

alongside the 'Cost-of-illness' code (see also Results, Section 3.3.2). The former issue (i) was identified in cases that eligibility criteria in the corresponding intervention review were numerous or complex (and thus a high level of detail was required to establish eligibility), as well as in cases that information relevant to assessments of eligibility was lacking in NHS EED or HEED records (more often observed in HEED records, in which the format and level of detail of included information appears to be more variable in comparison to standardised NHS EED structured abstract records).

On average, amongst those reviews with one or more eligible records/articles (and combining the total numbers of records and abstracts and/or full-text articles that needed to be examined in order to complete the processes of eligibility assessment and classification) this equates to an overall Number-Needed-to-Read of 31 per review (N= 10; Mean = 30.7, s.d.= 39.2; Range = 3.2 to 127.5).

Full details of unique and duplicate yields between NHS EED and HEED (eligible records/articles), by review, are provided in Appendix 3, Table A3.2. Amongst those reviews with one or more eligible records, the average (mean) numbers of records unique to NHS EED, records unique to HEED and duplicate records were 0.6 (N= 10; Mean = 0.6, s.d.= 0.5; Range 0 to 1), 1.5 (N= 10; Mean = 1.5, s.d.= 2.6; Range 0 to 8) and 3.0 (N= 10; Mean = 3.0, s.d.= 4.6; Range 0 to 15) respectively. This result illustrates the current value of conducting searches of both of these databases for the purpose of locating *all* available full and partial economic evaluations relevant to a Cochrane intervention review.

On average (median), amongst those reviews with one or more potentially eligible record following initial screening ('Screen 1'), further assessments of the eligibility of records/articles and their classification by type and framework of economic evaluation ('Screen 2') were completed in a total time of 22 minutes per review (N= 11; Median = 22.0; Mean = 29.6, s.d.= 34.7; Range = 2 to 118). Time taken to complete these processes was (unsurprisingly) correlated with the numbers of potentially eligible NHS EED and HEED records that passed initial screening ('Screen 1') (N = 11; Pearson correlation co-efficient = 0.97; $p<0.001$). The average (median) time taken to complete 'Screen 2' per potentially eligible NHS EED and HEED record ('Screen 1') was 5 minutes (N= 11; Median = 5; Mean = 5.1, s.d.= 2.0; Range = 2.0 to 8.3).

3.2.4. Total researcher time input to developing search strategies and processing search results for economic evaluations

On average (median), the aggregate researcher time input (time on task) to develop and apply NHS EED and HEED search strategies for relevant economic evaluations and to process the search results (where the latter comprises: initial screening of NHS EED and HEED records; assessment of eligibility based on NHS EED and HEED records and, if required, abstracts and/or full-text articles; and classification of eligible economic

evaluations) was 21 minutes per review (N= 36; Median = 21.0; Mean = 41.2, s.d.= 73.0; Range = 6.0 to 435.0). Amongst those reviews for which one or more eligible records/articles were identified (i.e. post 'Screen 2'), the average (median) total researcher time input (time on task) per eligible record/article was 17 minutes per review (N= 10; Median = 17.1; Mean = 22.9, s.d.= 17.1; Range = 6.7 to 66.5). The time input (time on task) allocated to complete these processes may be expected to double if recommended best practice of independent screening and classification by two researchers were applied (not taking into account any additional time required to discuss and resolve disagreements between the two researchers regarding eligibility and/or classification).

3.3. Searches for economic analyses containing relevant and potentially useful information on 'economic burden of condition' and/or 'cost-of-illness'

3.3.1. Formulating search strategies

The process of formulating search strategies for NHS EED and HEED, designed to capture records of economic analyses containing relevant and potentially useful information on the economic burden and/or cost-of-illness of the health condition addressed by the experimental intervention, was completed, on average (median), in 3 minutes (N= 30; Median = 3.0; Mean = 5.3; s.d.= 4.9; Range = 1.0 to 20.0) - see Appendix 2 for full details of search strategies. All of these NHS EED and HEED search strategies comprised search terms designed to capture 'Population' concepts only (since these search terms invariably included terms relating to the target 'health condition').

In addition to the two reviews that did not reproduce electronic search strategies designed to locate relevant studies of effects in the published review (Abdel-Aleem 2011, Eke 2011), search strategies executed in a further five reviews did not include any search terms designed to capture 'Population' concepts[22] (Birch 2011, Gurusamy 2011a, Jagannath 2011, Martin 2011, Morag 2011) and one EPOC review studied interventions to address healthcare performance rather than a health condition (Parmelli 2011). These eight reviews were therefore excluded from this part of the study.

3.3.2. Processing search results: 'Screen 1' (NHS EED and HEED records only)

On average (mean), the total number of records retrieved by searches for relevant and potentially useful economic analyses (economic burden/cost-of-illness) was 191 per review for NHS EED (N= 30; Mean = 190.6, s.d.= 220.1; Range = 0 to 876) and 158 per

[22] The omission of search terms designed to capture 'Population' concepts from search strategies designed to locate studies of effects is an entirely legitimate strategy in circumstances that search terms designed to capture other PICO concepts are judged sufficient (in terms of sensitivity and specificity of the search strategy) to locate all relevant studies.

review for HEED (N= 30; Mean = 158.0, s.d.= 141.7; Range = 1 to 473). Following initial screening of records sets for each database (i.e. screening based on the NHS EED or HEED record only), one or more potentially eligible records were identified for 70% of reviews (21 of 30).

Amongst reviews with one or more potentially eligible records, the average (mean) number of records that passed initial screening was 15 per review for NHS EED (N= 21; Mean = 15.4, s.d.= 16.7; Range = 0 to 64) and 14 per review for HEED (N= 21; Mean = 13.8, s.d.= 13.9; Range = 0 to 46). On average (mean), this equates to a Number-Needed-to-Read of 28 per review for NHS EED (N= 20; Mean = 27.9, s.d.= 28.6; Range = 6.3 to 118.0) and 47 per review for HEED (N= 20; Mean = 46.6, s.d.= 72.2; Range = 1.9 to 261.0) with respect to potentially eligible records.

Amongst reviews with one or more potentially eligible records, accounting for duplicate records, the average (mean) total number of potentially eligible articles was 23 per review for NHS EED and HEED combined (N= 21; Mean = 23.2, s.d.= 22.3; Range = 2 to 73). Full details of unique and duplicate yields between NHS EED and HEED (potentially eligible records), by review, are provided in Appendix 3, Table A3.5. Amongst those reviews with one or more potentially eligible records, the average (mean) numbers of records unique to NHS EED, records unique to HEED and duplicate records were: 9 (N= 21; Mean = 9.4, s.d.= 13.3; Range = 0 to 51), 8 (N= 21; Mean = 7.8, s.d.= 8.7; Range = 0 to 29) and 6 (N= 21; Mean = 6.0, s.d.= 6.2; Range = 0 to 22) respectively. Again, this provides an indication that, at present, there is value in conducting searches of both databases for this purpose.

On average (median), initial screening of records sets retrieved from both databases was completed in a total time of 38.5 minutes per review (N= 30; Median = 38.5; Mean = 38.0, s.d.= 27.9; Range = 0 to 85). Time taken to complete this process was again (unsurprisingly) correlated with the size of retrieved records sets (N = 30; Pearson correlation co-efficient = 0.79; $p<0.001$). The average (median) time taken to screen a single NHS EED or HEED record ('Screen 1' only) was approximately 8 seconds (N= 27; Median = 0.14 mins; Mean = 0.14 mins, s.d.= 0.08; Range = 0.03 to 0.42 mins).

3.3.3. Processing search results: 'Screen 2' (Assessment of eligibility based on article abstracts and/or full-texts and classification of eligible records/articles by type of economic evaluation)

Following the second stage of screening (i.e. assessment of eligibility based on the abstract and/or full-text of the corresponding article - conducted only for articles potentially relevant and useful to those intervention reviews selected for development

of economic commentaries), the number of eligible articles[23] was, on average (mean), 23 per selected review after removal of duplicates (N= 5; Mean = 23.6, s.d.= 24.9; Range = 0 to 66).

Classification of eligible records/articles by type of economic analysis revealed that the most frequently eligible type of analysis was a cost-of-illness analysis conducted within the framework of an applied study (50%, 58 of 117), followed by a review of applied cost-of-illness analyses (26%, 30 of 117). The full classification of eligible records/articles by type of economic analysis is provided in Appendix 3, Table A3.7. As with economic evaluations (see Results, Section 3.2.3), these figures do not exclude those articles reporting analyses that are, in some sense, non-independent.

The processes of assessing the eligibility of records/articles with respect to inclusion and/or exclusion criteria set for each selected review, and their classification by type of economic analysis, required retrieval and examination of the corresponding abstract and/or full text article (i.e. could not be completed based on the NHS EED and/or HEED record alone) in 52% of cases (61 of 117 – see also Appendix 3, Table A3.8). Examination of the corresponding abstract and/or full-text article was almost invariably required for these purposes in the case of articles that had an NHS EED but not a HEED record, since all NHS EED records of applied cost-of-illness studies (classified as 'Cost studies' in NHS EED terminology) and reviews of applied cost-of-illness studies (classified as 'Reviews of economic evaluations' in NHS EED terminology) are citation only records (i.e. they do not include any additional information beyond bibliographic details of the corresponding article). Examination of the abstract and/or full text article was also required in the case of some HEED records that provided insufficient detail regarding the study design to allow classification to be made with confidence (see also 'Results', Section 3.2.3).

Combining the total numbers of records and abstracts and/or full-text articles that needed to be examined in order to complete the processes of eligibility assessment and classification (so far as possible), this equates, on average (mean), to an overall Number-Needed-to-Read of 21 per selected review for NHS EED and HEED combined (N= 4; Mean = 21.3, s.d.= 15.6; Range = 6.5 to 40.8).

Full details of unique and duplicate yields between NHS EED and HEED, with (eligible records/articles), by selected review, are provided in Appendix 3, Table A3.6. Amongst selected reviews with one or more potentially eligible records, the average (mean) numbers of records unique to NHS EED, records unique to HEED and duplicate records

[23] As well as records/articles whose eligibility could be established with confidence, figures for 'eligible records/articles' includes any potentially eligible records/articles that could not be excluded with confidence following this second round of screening, because the NHS EED and/or HEED record was 'citation only' and either the abstract nor full-text of the corresponding article could be retrieved, or only the abstract could be retrieved and the record/article still could not be excluded with confidence.

were: 15 (N= 4; Mean = 14.5, s.d.= 17.5; Range = 0 to 39), 9 (N= 4; Mean = 8.5, s.d.= 6.1; Range = 1 to 16) and 7 (N= 4; Mean = 6.5, s.d.= 4.2; Range = 0 to 11) respectively.

On average (median), assessments of the eligibility of records/articles and their classification by type of economic analysis ('Screen 2' only) were completed in a total time of 54 minutes per selected review (N= 5; Median = 54.0; Mean = 55.0, s.d.= 46.9; Range = 0 to 128). Time taken to complete these two processes ('Screen 2') was again (unsurprisingly) correlated with the number of potentially eligible NHS EED and HEED records that passed initial screening ('Screen 1') (N = 5; Pearson correlation co-efficient = 0.99; p=0.01). The average (median) time taken to complete 'Screen 2' per potentially eligible NHS EED and HEED record ('Screen 1') was 3.1minutes amongst selected reviews (N= 4; Median = 3.1; Mean = 3.2, s.d.= 1.3; Range = 1.8 to 4.9).

3.3.4. Aggregate researcher time input to developing search strategies and processing search results for economic analyses

On average (median), the aggregate researcher time input (time on task) to develop and apply NHS EED and HEED search strategies for relevant and potentially useful economic analysis (economic burden/ cost-of-illness) and to process the search results (where the latter comprises: initial screening of NHS EED and HEED records; assessment of eligibility based on NHS EED and HEED records and, if required, abstracts and/or full-text articles; and classification of eligible analyses) was 101 minutes per selected review (N= 5; Median = 101.0; Mean = 109.4, s.d.= 76.1; Range = 4.0 to 209.0). Amongst those reviews for which one or more eligible records/articles were identified (i.e. post 'Screen 2'), the average (median) total researcher time input (time on task) per eligible record/article was 6 minutes per selected review (N= 4; Median = 5.7; Mean = 5.6, s.d.= 2.0; Range = 3.2 to 7.8).

As with economic evaluations (see Results, Section 3.2.4), the time input (time on task) allocated to complete these processes may be expected to double if current recommended best practice of independent screening and classification by two researchers were applied. However, time input (time on task) required to complete these processes would be reduced if recommendations of this study are followed (see 'Discussion and recommendations').

3.4. Development of economic commentaries

3.4.1. Selected reviews

The five reviews selected for development of economic commentaries are listed in Table 1, below.

Table 1. Reviews selected for development of economic commentaries

First author/ year	*Title*	*CRG*
Kamal 2011	Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin	Stroke Group
Brito 2011	Factor Xa inhibitors for acute coronary syndromes	Heart Group
Dasari 2011	Laparoscopic versus open surgery for small bowel Crohn's disease	Colorectal Cancer Group
Wildschut 2011	Medical methods for mid-trimester termination of pregnancy	Fertility Regulation Group
Komossa 2011	Risperidone versus other atypical antipsychotics for schizophrenia	Schizophrenia Group

3.4.2. Economic commentaries

Appendix 4, Tables A4.1 and A4.2 provide (for the 5 selected reviews) full reference lists of articles reporting: (i) relevant full and partial economic evaluations and (ii) economic analyses containing relevant and potentially useful information on the economic burden or cost-of-illness of the health condition addressed by the experimental intervention(s). Appendix 4, Tables A4.1 and A4.2 also record whether each eligible record/article was retrieved as an: NHS EED record (structured abstract record); NHS EED record (citation only record); HEED record (field-coded abstract record); HEED record (citation only record); article abstract; article full-text.

These tables also highlight articles used to inform development of the economic commentaries presented below. Used articles are also cited in the economic commentaries. NHS EED and HEED records of used articles are provided in Appendix 5. In the case of economic evaluations, all eligible records/articles were used to inform development of each economic commentary. In the case of economic analyses (economic burden/ cost-of-illness), small numbers of the most useful analyses were selected to inform development of each economic commentary (see 'Discussion and recommendations').

Five economic commentaries are provided in boxes below. Text that is reproduced verbatim from the published review (i.e. the original 'Background' and 'Discussion' sections) is displayed in plain type (i.e. no highlighting). Economic commentary summarising information that is only available in NHS EED records is highlighted in yellow. Economic commentary summarising information that is only available in HEED

records is highlighted in green. Economic commentary summarising information that is available in both NHS EED and HEED records is highlighted in pink. Economic commentary summarising any useful additional information only available in article abstracts and/or full texts is highlighted in turquoise. Economic commentary based on (but not summarising) information drawn from across all available sources is highlighted in grey.

Kamal 2011

BACKGROUND

Description of the condition

Stroke is the leading cause of sustained disability in the world today, placing a huge economic burden on health systems and society. Typically, 3% of a country's total health expenditure is attributable to all-cause stroke treatment - a figure that typically represents 0.2–0.3% of gross domestic product – (Evers 2004, cited in Flynn 2008). The wider societal costs have been estimated at $62.7 billion (2007 USD) in the US and €34 billion (2003 EUR) across EU member states (Flynn 2008).

Two-thirds of all strokes now occur in the developing world (Lopez 2006). It is important to study interventions that are relevant to the Asian population as it bears the brunt of the burden of global stroke mortality (Feldmann 1990). Moreover the distribution of types of strokes is different in this region, with a significantly higher proportion of intracranial haemorrhages (ICH) than in the developed world (Liu 2007). Individuals suffering from stroke are already at a very high risk of developing subsequent stroke (Wong 2002). In addition, they are at higher risk of morbidity from other clinical manifestations of atherosclerotic disease such as myocardial infarction (MI), angina or peripheral arterial disease (PAD) (Burke 1995). Although aspirin is beneficial for the secondary prevention of a wide spectrum of cardiovascular incidents, including stroke, it is also known to be associated with a risk of ICH. Cilostazol, a phosphodiesterase type 3 (PDE3) inhibitor, has been tested in this population for secondary stroke prevention and appears to contribute to fewer intracranial haemorrhages than with aspirin while maintaining a significant reduction in the risk of recurrent strokes. In the Cilostazol Stroke Prevention Study, a phase III clinical trial involving more than 1000 Japanese patients, cilostazol was found to reduce the risk of secondary stroke by 41.7% compared with placebo (Matsumoto 2005). In a phase II clinical trial comparing the efficacy of cilostazol versus aspirin among 720 Chinese patients, stroke recurrence was reported in 12 patients in the cilostazol group and in 20 patients in the aspirin group. The estimated hazard ratio was 0.62 (95% confidence interval (CI) 0.30 to 1.26; P = 0.185). Also, cerebral haemorrhagic events were significantly more common in the aspirin group than in the cilostazol group (7 versus 1; P = 0.034) (Huang 2008).

Description of the intervention

Cilostazol is a selective and potent phosphodiesterase type 3 (PDE3) inhibitor (Minami 1997) that is both an antiplatelet and a vasodilating agent. PDE 3 increases the breakdown of cyclic adenosine monophosphate (cAMP) (Ikeda 1999). Inhibition of PDE3 increases the levels of cAMP. Since both platelets and vascular smooth muscle cells contain PDE 3A, inhibition leads to decreased platelet aggregation. Cilostazol inhibits the uptake of adenosine (Liu 2000). This leads to an enhanced adenosine action

via A1 and A2 receptors. In platelets and vascular smooth muscle cells A2 mediated increases in cAMP enhance the consequences of PDE inhibition, that is result in additional increases in cAMP. Aspirin is a non-selective irreversible inhibitor of cyclooxygenase (COX) and has anti-inflammatory and antiplatelet effects. It decreases the formation of prostaglandins (PGs) and thromboxanes, which leads to decreased platelet aggregation and stabilization (Abramson 1989).

How the intervention might work

In addition to platelet inhibition, cilostazol has other effects on the circulatory system that may be relevant to stroke prevention. Both PDE inhibition and possibly inhibition of adenosine uptake act in concert to relax vascular smooth muscle cells and lead to vasodilatation. Monocyte chemoattractant protein 1 (MCP- 1) plays a significant role in mediating monocyte recruitment in atherosclerotic lesions. Interestingly, cilostazol also inhibits the cytokine induced expression of MCP-1 probably due to cAMP elevation, which might contribute to an anti-inflammatory action (Nishio 1997).

Cilostazol acts as an antimitogenic agent by several mechanisms. It blocks the surface expression of the platelet fibrinogen receptor (G2b/3a) as well as alpha-granule secretion of P-selectin (Inoue 1999). P-selectin is assumed to be involved in platelet dependent mitogenesis. This effect might contribute to inhibition of re-stenosis. Heparin binding epidermal growth factor (HBEGF), which is also inhibited by cilostazol, is one the most potent mitogens for vascular smooth muscle cells and is found in macrophages and vascular smooth muscle cells (Kayanoki 1997). Cilostazol used for a period of 12 weeks has been shown to increase high density lipoproteins (HDL) by 10% and decrease triglycerides by 15% (Elam 1998). These multiple potential mechanisms of action may explain the efficacy of cilostazol.

Why it is important to do this review

Cilostazol has shown promise as an alternative to aspirin for Asian populations with ischaemic stroke (Shinohara 2008). The risk of primary intracranial haemorrhage (ICH) in people from these regions is 30% compared to 10% in the developed world (Liu 2007). Cilostazol appears to prevent more ischaemic strokes and cause less ICH than aspirin when used for secondary prevention of ischaemic stroke (Huang 2008).

Aspirin is the most widely prescribed agent for the prevention of stroke in the world today (Rother 2008). Aspirin overall reduces **t**he risk of major vascular events by 13% (95% CI 6% to 19%) (Algra 1996). A study of 720 Chinese patients that compared treatment with a standard dose of aspirin at 100 mg per day to cilostazol 100 mg twice a day was associated with a reduction of recurrent stroke by 30% (95% CI -26% to 70%) (Huang 2008). A systematic review is necessary to evaluate the strength of these claims.

DISCUSSION

Summary of main results

We undertook this review to determine if, compared to aspirin, cilostazol is a better alternative for secondary prevention of vascular events in patients with a previous ischaemic stroke or TIA. We analysed the available data from two randomised trials directly comparing cilostazol to aspirin. The larger trial (CSPS II 2010) contributed about 80% of the patients randomised. It studied patients at high vascular risk (those with previous TIA or ischaemic stroke of arterial origin) and primarily evaluated the outcome of stroke of all types, with ischaemic stroke, death formal causes and a composite outcome as secondary endpoints. It also examined safety endpoints in terms of all significant haemorrhagic events. The smaller study, contributing about 20% of patients (CASISP 2008), assessed the composite outcome of vascular events (stroke, MI, and vascular death) and provided adequate data on each subtype of vascular events, along with outcomes of safety.

Combining the main outcome of serious vascular events into a composite outcome of stroke, MI and vascular death not only increases the statistical power and reliability of the analysis, but also provides a more cohesive measure of effectiveness. Analysis revealed that, compared to aspirin, cilostazol is significantly more effective in preventing vascular events (stroke, MI and vascular death) and stroke of all types, in patients with a history of stroke or TIA. Cilostazol showed an overall reduction in the composite outcome of 28%, ranging between 9% to 43% (95% CI), which corresponds to comparative avoidance of 26 events (ranging between nine to as high as 40 events) per 1000 patients treated for an average of three years. Thus for each vascular event to be prevented, 39 patients needed to be treated with cilostazol for an average of three years compared with aspirin, with a wider range of between 26 and 117 patients per event (95% CI).

In patients with a previous history of stroke or TIA, the proportional benefit of cilostazol over aspirin on the outcome of strokes of all type was very similar to that of the composite outcome of vascular events. Cilostazol demonstrated a reduction of about 33% (14% to 48%) compared with aspirin, corresponding to comparative avoidance of 27 events (95% CI 12 to 41) per 1000 patients treated for an average of three years. Thus for each stroke event to be prevented, the number needed to treat (NNT) for an average of three years with cilostazol was 37 patients (95% CI 25 to 87) when compared to aspirin. Since it is known that in patients with previous history of stroke or TIA (that is patients at highest risk for subsequent vascular events) the greatest risk is of stroke, the composite outcome is bound to heavily reflect that outcome in terms of stroke of all types.

On subgroup analysis, cilostazol showed a 20% reduction in recurrence of ischaemic stroke subtypes compared with aspirin. Although this result was not statistically

significant, it did indicate non-inferiority of cilostazol compared with aspirin in terms of secondary prevention of ischaemic stroke. In relation to haemorrhagic stroke during follow up, cilostazol showed an outstanding risk reduction of 74% (95%CI 45%to 87%) compared to aspirin, thereby demonstrating its safety and tolerability in a population that is inherently at higher risk of intracerebral haemorrhage.

In terms of adverse effects, the results of the review showed that cilostazol had a significantly higher adverse effect profile than aspirin, in terms of all other outcomes of safety including headache, gastrointestinal intolerance, palpitations, dizziness and tachycardia. In both trials (CASISP 2008; CSPS II 2010) it was noted that more recruited patients discontinued cilostazol compared with aspirin as a consequence of adverse drug reactions. Results from the CSPS II trial (CSPS II 2010) were inconclusive in terms of cardiac adverse effects, namely angina and cardiac failure, while CASISP (CASISP 2008) did not note any such events.

In safety analyses, aspirin caused more intracranial haemorrhage, extracranial haemorrhage and GI haemorrhage but, evaluated as separate outcomes, only extracranial haemorrhage was significantly higher in patients on aspirin compared with cilostazol. All of these outcome events were addressed specifically in both included trials. The CASISP 2008 trial reported symptomatic intracerebral haemorrhage along with two events of asymptomatic intracerebral haemorrhage with aspirin that were included in our analysis. Observational studies conclude that cilostazol shows no evidence of an increase in any bleeding abnormality (CSPS 2000). Therefore, it can be stated with a certain degree of reliability that cilostazol is associated with a lesser risk of bleeding events than aspirin.

Overall completeness and applicability of evidence

The two studies included in the review were double-blind randomised controlled trials that reported relevant outcome data. In CSPS II 2010 outcomes were assessed via clinical record review carried out by an independent data monitoring committee. These patients were regularly reviewed at six-month intervals for safety, adherence, and drug tolerability. The participants were all Asians and the maximum age at enrolment was 79 years. Importantly, the included strokes were all atherothrombotic (large vessel atherosclerosis and lacunes) in origin, and there were no patients with cardioembolic strokes recruited in these trials. A relevant patient exclusion criterion was the absence of associated cardiovascular disease.

These studies show us that in the above populations and settings, cilostazol is relatively superior to aspirin in terms of a composite outcome of stroke, MI, and vascular death in Asian patients with stroke of arterial origin. Since Asians are at higher risk of intracerebral haemorrhage, and cilostazol-treated Asians had significantly fewer intracerebral haemorrhages than their aspirin-treated counterparts, cilostazol is a safer option in this setting.

With regard to patients with concomitant cardiovascular disease, the outcome of safety in terms of cardiac adverse effects of cilostazol compared with aspirin cannot be assessed in this review since patients with cardiovascular disease were excluded in both trials. Hence, it is clinically important to exclude cardiovascular disease in stroke patients prior to initiating cilostazol.

No comparator groups were available to compare for subgroup analysis. Stroke studies from other ethnic populations, including Caucasians, are needed to provide general applicability.

The dose used in the CASISP 2008 trial was fairly high at 200 mg twice daily, while lower doses of 100 mg twice daily were used in CSPS II 2010. Studies show that lower doses of cilostazol are associated with fewer headaches requiring discontinuation, where

3.7% of patients on 100 mg twice daily required hospitalisation compared to 1.3% on 50 mg twice daily (Robless 2008). Thus, to reduce the side-effect profile of cilostazol, it could be recommended to administer cilostazol in incremental doses starting from a minimum of 50 mg twice daily.

Cilostazol is more expensive than aspirin. Each cilostazol tablet costs 10 times more than that of aspirin, and bearing in mind that cilostazol requires double dosing, this makes each dose of cilostazol 20 times more costly compared with aspirin. To prevent one extra vascular event, 39 patients (95% CI 26 to 117 patients) need to be treated with cilostazol for a period of three years compared to aspirin. Whether this justifies prolonged treatment in resource strapped settings needs further cost-benefit analysis.

To supplement the main systematic review of effectiveness and safety, we sought to identify economic evaluations of cilostazol, compared with aspirin, for secondary prevention of vascular events after stroke of arterial origin in Asian patients. Systematic supplementary searches of the NHS Economic Evaluation Database and the Health Economic Evaluations Database identified just one relevant economic evaluation. This was a cost-utility analysis, conducted within the framework of a decision model (Markov model), that compared the use of 200 mg/day cilostazol with both use of 81 mg/day aspirin and no prophylaxis in a hypothetical cohort of 65-year-old Japanese men following first-ever ischaemic stroke (Inoue 2006). The economic analysis adopted a third-party payer analytic perspective (Japanese publicly funded health insurer) and a lifetime time horizon. Direct costs included in the analysis were those of the health care system, comprising the costs of drugs, treatment for gastrointestinal bleeding, treatment for recurrence of cerebral infarction, and long-term care following recurrence. With respect to clinical effectiveness and safety, the authors used a meta-analysis and a double-blind randomised controlled trial to derive the recurrence rates for stroke and adverse events, and the results from one trial to derive the rates of haemorrhagic adverse events. The natural death rate at each stage was derived from

Japanese life tables, while mortality rates after cerebral infarction recurrence were derived from data from a Japanese prefecture. Utility values were derived from Barthel Index values. The economic analysis found that no prophylaxis was dominated by the aspirin strategy (i.e. the aspirin strategy was both cheaper and more effective than no prophylaxis). In the base case scenario, compared with aspirin, the additional cost per quality adjusted life year (cost per QALY) gained using the cilostazol strategy was ¥1.79 million (JPY 2004). The results of a Monte Carlo simulation on utility values showed that the minimum incremental cost-utility ratio was ¥J 1.78 million (JPY 2004) and the maximum was ¥2.05 million (JPY 2004) for cilostazol compared with aspirin. The authors conclude that, from the perspective of a Japanese publicly funded health insurer, incremental cost-utility ratios for cilostazol versus aspirin appear reasonable at conventional levels of willingness-to-pay for an additional QALY (since a £30,000 threshold equated to approximately ¥5.6 million, 2004 JPY).

We did not subject the identified economic evaluation to critical appraisal and we do not attempt to draw any firm or general conclusions regarding the relative costs or efficiency of cilostazol versus aspirin. However, the available economic evidence indicates that, from an economic perspective, use of cilostazol is (at least) a promising strategy compared with aspirin for the secondary prevention of ischaemic stroke in Asian male patients. End users of this review will need to assess the extent to which methods and results of the identified economic evaluation may be applicable (or transferable) to their own setting.

Quality of the evidence

Overall the included evidence is based on well-designed trials.

Potential biases in the review process

The potential bias is that the data are restricted to Asians.

Agreements and disagreements with other studies or reviews

This review is in line with the general studies and reviews on this topic.

Brito 2011

BACKGROUND

Acute coronary syndromes (ACS) are life-threatening disorders which remain as a common cause of cardiovascular morbidity and mortality, accounting for half of all deaths due to cardiovascular diseases and contributing to high economic burden to global health care systems (ACC/AHA 2009; ACCP 2008; ESC Guideline 2007), in terms of both direct health care costs and indirect, social and economic costs (Turpie 2006) that continue to be incurred long after the acute event has resolved (Shetty 2008).

One study estimated that the total direct US healthcare costs associated with management of coronary heart disease (CHD) in 2006, most of which consisted of costs for ACS, were $75.2 billion (comprising $11.1 billion for physician and other professional costs; $41.8 billion for hospital costs; $10.9 billion for nursing-home costs; $9.8 billion for the cost of drugs and other medical durables; and $1.6 billion for home healthcare costs) (Turpie 2006). The same study estimated that indirect US costs associated with CHD in 2006 (due to lost productivity) were $142.5 billion. Another study estimated the total direct healthcare costs associated with management of ACS during the first year following diagnosis at €1.9 billion in the UK (2004 Euros), compared with €1.3 billion in France, €3.3 billion in Germany, €3.1 billion in Italy and €1.0 billion in Spain, accounting for between 0.9% and 2.9% of total healthcare expenditure in these countries (Taylor 2007), and with pharmaceutical expenditure contributing a 14-25% of total direct healthcare costs.

ACS includes three clinical entities: unstable angina, non ST-elevation myocardial infarction (Non-STEMI) and ST-elevation myocardial infarction (STEMI) (ESC Guideline 2007). The syndromes are the result of vulnerable atherosclerotic plaques with high risk of fissures or erosion, leaving large areas of the subendothelial connective tissue of the plaque exposed, which predisposes to development of a total or partially occlusive thrombus as a consequence of the exposure to the thrombogenic blood stream constituents (ACC/AHA 2007; Davies 2000;Hamm 2000).

The appropriate management of ACS requires intensive medical therapy often associated to invasive cardiovascular procedures. Since the patients with the disorder exhibit high levels of markers produced by thrombin generation, the activation of coagulation mechanisms seems to play a central role in the pathogenesis of ACS (ACCP 2008; Bonaca 2009). According to this, the administration of unfractionated heparin (UFH) and low molecular weight heparins (LMWH) in the treatment of unstable angina and Non-STEMI has the objective of inhibiting thrombin generation and/or preventing the progression of thrombus formation, via their activity in accelerating the activation of the proteolytic enzyme antithrombin, an inhibitor of anticoagulation factors IIa, Ixa, and Xa (ACC/AHA 2007; Hamm 2000). In STEMI, heparins are used as an adjuvant

therapy to fibrin-specific thrombolytic agents in order to avoid paradoxical activation of the blood coagulation cascade (ACC/AHA 2009; ESC Guidelines 2008;Goodman 2008).

Although UFH and LMWH have shown clinical efficacy and safety, some limitations are associated with their use. The pharmacokinetic profile of UFH is characterized by poor bioavailability at low doses and short half life via the subcutaneous route, which determine its intravenous route necessary. Moreover, after treatment discontinuation, the recurrence of clinical events as a consequence of reactivation of the coagulation process has been described (ACCP 2008). On the other hand, enoxaparin, a LMWH, has a predictable dose-effect relationship so it is effectively administrated subcutaneously without the need to monitor activated partial thromboplastin time (aPTT or APTT), although its intravenous administration is necessary in urgent situations because its maximum plasma levels occur three to five hours after subcutaneous administration (ACCP 2008). It must also be noted that enoxaparin is associated with a lower risk of thrombocytopenia and osteoporosis than UFH, but with a higher frequency of minor bleeding as well as some uncertainty about its use in obese subjects and patients with renal insufficiency, particularly if creatinine clearance is lower than 30 mL/min. Therefore monitoring of its plasma levels may be useful in these special populations to avoid inadequate drug concentrations during treatment (Bassand 2008; Lim 2006; McCaan 2008;Warkentin 2008).

To overcome the limitations of these anticoagulants, development of new synthetic agents with better efficacy and safety profiles has been pursued (Bassand 2008; Hirsh 2005). These new agents target the inhibition of anticoagulation by blocking its initiation through preventing thrombin generation or inhibiting thrombin action (ACCP 2008; Barantke 2008). Inhibitors of activated factor X (Xa), such as fondaparinux, exert their antithrombotic activity by selectively binding to the co-factor antithrombin to induce the neutralization of factor Xa (Blick 2008). Neutralization of factor Xa interrupts the blood coagulation cascade and thus inhibits thrombin generation and thrombus development (Hirsh 2005). Xa inhibitors also prevent the interaction of factor Xa with other substrates by binding directly to its active sites (Barantke 2008; Comp 2003).

These newer synthetic agents may have numerous potential advantages compared to UFH or LMWH, such as having no requirement to monitor coagulation parameters because there is no binding to plasma proteins, and low drug interactions which allows a predictable dose-effect ratio and an easier administration regimen (Crowther 2004; Eikelboom 2010; Hirsh 2007). The most common adverse effect reported with the use of Xa inhibitors has been major/minor bleeding (major 2.7%, minor 3%) and secondary local bruising, which in clinical trials have been reported doubled in patients weighing less than 50 kg (Brown 2007). The absence of thrombocytopenia with the use of fondaparinux makes it an attractive alternative (Franchini 2005). Nevertheless, the future role of these new anticoagulants and their clinical utility and safety profiles in the treatment of ACS is still a matter of current investigation (Crowther 2004; Eikelboom

2010; Franchini 2005; Hirsh 2007; Linkins 2005; Warkentin 2008).

In this review we systematically reviewed the evidence and data available to investigate the impact of Xa inhibitors in the management of unstable angina, Non-STEMI and STEMI.

DISCUSSION

Since arterial thrombosis has a principal role in ACS, antithrombotic therapy is pivotal to avoid total or partial vessel occlusion by the developing thrombus (Maan 2009). UFH has been the main antithrombotic agent to reduce the occurrence of major ischemic events in ACS for nearly 60 years, but its usage requires careful monitoring and adverse effects include thrombocytopenia and osteoporosis (ACCP 2008). This prompted the development of new antithrombotic agents such as LMWH and factor Xa inhibitors (ACCP 2008; Eikelboom 2010; Harm 2007; Hirsh 2007).

Summary of main results

A number of studies evaluating the role of factor Xa inhibitors in ACS has not been included in our review because their methodological characteristics were not suitable (Alexander 2005; Cohen 2007) or because trial data are yet to be published (e.g. Sabatine 2009). Therefore, our review is not a complete representation of all the available evidence on the clinical efficacy and safety profiles of factor Xa inhibitors.

Fondaparinux, an indirect factor Xa inhibitor, when administrated in the beginning of ACS development (six to eight days) showed an effect in reducing all-cause mortality at 30 days compared against enoxaparin, but we concluded that there was possibly no significant impact on the clinical outcome. However, a long-term reduction of mortality at 90 to 180 days was apparent, especially when compared to enoxaparin, resulting in an NNTB of at least 126. Fondaparinux did not reduce the risk of non-fatal AMI or re-infarction at 9 and 30 days, neither did it reduce the incidence of combined endpoint of all-cause mortality and non-fatal AMI at nine days. Use of low dose fondaparinux showed equivalent effect in reducing the risk of all-cause mortality, non-fatal AMI or re-infarction at 9 days to UHF or enoxaparin.

For participants undergoing PCI, fondaparinux demonstrated similar clinical efficacy on the risk of all-cause mortality, non-fatal AMI or re-infarction at 30 days to UFH or enoxaparin. On the other hand, an increased risk of catheter thrombosis was clearly associated with the use of fondaparinux.

Our results indicate that the factor Xa inhibitor fondaparinux might be a safe alternative to enoxaparin in terms of the risk of minor and major bleeding at 30 days, but this was not evident when compared to UFH. This could be useful amidst concerns associated with an increased risk of bleeding related to their use (Brown 2007).

Overall completeness and applicability of evidence

In addition to their clinical effectiveness and safety profile, the newer antithrombotic agents need to be more economically attractive than UFH (Nutescu 2006). Health economic analyses on fondaparinux have been limited to secondary cost-effectiveness analyses, based on data from published RCT as well as analytical models such as decision trees or Monte Carlo modelling; fondaparinux appeared to be cost-effective in participants with non-STEMI when compared against enoxaparin (Latour-Perez 2009; Maxwell 2009; Yusuf 2006 OASIS 5).

Quality of the evidence

The limitations related to the assignment of the participants to one of the two control groups in Yusuf 2006 OASIS 6 and the lack of blinding of participants in Coussement 2001 could be potential sources of bias. The external validity in Yusuf 2006 OASIS 6 could be affected because the stratification of the control group to receive UFH or placebo was achieved based on the investigator's judgment other than randomization. In Coussement 2001, absence of blinding led to an adjusted dose-finding study. Nevertheless, in both cases, the confidence in the resulting outcomes of interest seemed not to be affected by these shortcomings in our analyses.

The presence of heterogeneity in some of the outcome analyses could be explained by the diverse methodological designs of the studies, including varied agents used in the treatment and control groups, as well as different co-morbidities in the included participants.

All the studies were sponsored by pharmaceutical companies associated with the study drug, or the authors received research support or consultant fees from the pharmaceutical companies related to it. There was no rational evidence to suggest the results published could be seriously affected. Nonetheless, the data presented should be interpreted with caution.

Potential biases in the review process

A broad and systematic literature search for potentially relevant studies was performed. This was followed by careful selection of eligible studies based on set inclusion/exclusion criteria. We evaluated the risk of publication bias using funnel plots. However, interpretation of these should be done cautiously because the number of studies included in relation to our selection criteria was limited. Therefore, although there was asymmetry in our funnel plots, it was possibly due to methodological heterogeneity and not due to publication bias.

Agreements and disagreements with other studies or reviews

Numerous overviews have recently focused on the potential role of factor Xa inhibitors in ACS by reviewing studies that have investigated the clinical effectiveness and safety of these new agents (Barantke 2008; Bonaca 2009). Similar to our findings, these overviews concluded that factor Xa inhibitors were not inferior to UFH and enoxaparin

in reducing the risk of death, AMI, re-infarction, or recurrence of ischemia at 30 days. However, substantial reduction was seen in mortality rates at 180 days as well as in major and minor bleeding when factor Xa inhibitors were compared to enoxaparin. This reduced association of factor Xa inhibitors with adverse bleeding was thought to be caused by two potential factors: a lack of thrombin interference, or the relatively low dose that were deemed effective compared to standard enoxaparin dosage (ACC/AHA 2007; Bonaca 2009; Karthikeyan 2009).

Published reviews on the role of factor Xa inhibitors in ACS all commented on their use in patients undergoing PCI as well as cost effectiveness (ACCP 2008; Barantke 2008; Bonaca 2009; Karthikeyan 2009). The increased risk of catheter thrombosis associated with factor Xa inhibitors in the patients undergoing PCI could be explained by the unavoidable contact-pathway activation triggered by contact of the blood to catheters during PCI. This finding is in agreement with ours. UFH was useful in inhibiting contact coagulation through factors XIa and XIIa inhibition (Bonaca 2009; Karthikeyan 2009). Consequently, it was recommended that fondaparinux should be administered in adjunction to UFH for patients undergoing invasive treatments such as PCI (ACC/AHA 2007; ACC/AHA 2008; ESC Guideline 2007; ESC Guidelines 2008). Nevertheless, more substantial data from well-planned trials in appropriate settings are needed.

Economic evidence

To supplement the main systematic review of efficacy and safety of factor Xa inhibitors in the treatment of ACS, we sought to identify economic evaluations in which factor Xa inhibitors are compared with other anticoagulant strategies. Systematic supplementary searches of the NHS Economic Evaluation Database and the Health Economic Evaluations Database identified three such economic evaluations. Two cost-utility analyses (decision models) compared subcutaneous (SC) fondaparinux (2.5mg/day) with SC enoxaparin (1mg/kg 12 hourly) in patients with non ST-elevation myocardial infarction, pre-treated with triple antiplatelet therapy and early revascularization in Spain and the US respectively (Latour-Perez 2009, Sculpher 2009). Both analyses utilised comparative effectiveness and safety data collected from the OASIS-5 trial (Yousef 2006). Both adopted a health care provider perspective and modelled costs and quality adjusted life years (QALYs) over the patients' lifetime. Both analyses found that fondaparinux dominated enoxaparin (i.e. was both less costly and generated more QALYs) over the patients' lifetime, in most scenarios considered, and across all levels of baseline risk.

A cost-effectiveness analysis (decision model) compared four anticoagulation strategies (UFH with a glycoprotein inhibitor; enoxaparin with a glycoprotein inhibitor; bivalirudin alone; and fondaparinux with a glycoprotein inhibitor) in patients with non-ST-elevation acute coronary syndrome (Maxwell 2009) in US secondary care. This analysis utilised clinical evidence collected from three RCTs, including the OASIS-5 trial (Yousef 2006). It adopted a health care provider perspective but the time horizon was

not reported. The analysis found that bivalirudin and fondaparinux were superior in most scenarios considered and the authors concluded that bivalirudin was the least costly anticoagulation therapy amongst those compared for early invasive treatment, with fondaparinux preferred for patients undergoing conservative treatment.

We did not subject the three identified economic evaluations to critical appraisal and we do not attempt to draw any firm or general conclusions regarding the relative costs or efficiency of the anticoagulation strategies compared. However, evidence collected from these economic evaluations indicates that, from an economic perspective, use of fondaparinux is (at least) a promising strategy compared with other anticoagulation strategies in patients with non-ST-elevation acute coronary syndrome. End users of this review will need to assess the extent to which methods and results of identified economic evaluations may be applicable (or transferable) to their own setting.

Dasari 2011

BACKGROUND

Crohn's disease (CD) is a common chronic inflammatory bowel disease usually characterised by patchy granulomatous inflammation of whole thickness of bowel that can affect any part of gastrointestinal tract. The incidence of CD is 5-10 per 100 000 per year with a prevalence of 50-100 per 100 000 (Carter 2004). Clinical patterns include combined small and large intestinal pattern (26% to 48%), small intestine only pattern (11% to 48%) and colon only pattern (19% to 51%) (Munkholm 2004). Of these, involvement of terminal ileum and colon is the most common pattern (55%). Involvement of duodenum, oesophagus, stomach and mouth is uncommon and this rarely occurs without concurrent disease activity in the small bowel and / or colon (Thoreson 2007).

The economic burden of CD to society is substantial, comprising both direct medical costs and indirect costs (e.g. loss of work including sick leave, early retirement, reduced employment, and early mortality; reduced productivity of paid work; and loss of leisure time) (Yu 2008). A recent review of applied studies on the costs of CD in the United States and other Western countries estimated the economic burden of Crohn's disease at between $10.9billion and $15.9 billion (2006 USD) in the United States and between €2.1 billion and €16.7 billion (2006 EUR) in Europe (Yu 2008). The authors concluded that hospitalization costs are the largest driver of direct medical costs and that cost-of-illness differs substantially by disease severity, with costs amongst patients with severe disease 3- to 9-fold higher than patients in remission (Yu 2008).

Patients with small bowel CD commonly present with an acute exacerbation characterised by abdominal cramps, diarrhoea, malaise and loss of weight that is primarily managed medically using steroids, immunomodulators (Azathioprine, Mercaptopurine, Methotrexate) or biological therapy (anti-TNF agents) (Travis 2006). Surgical treatment is required in approximately 70 percent of patients (Fazio 1993) for failed medical therapy, recurrent intestinal obstruction, malnutrition and for septic complications (free perforation, abscess). Reoperation is required in 70 to 90 percent of all patients and multiple procedures in more than 30 percent (Duepree 2002) but the disease remains incurable. Resection and anastomosis is indicated for short segment with multiple strictures or active disease, diseased bowel with fistula, abscess or phlegmon. Strictureplasty is a safe and effective alternative to bowel resection in view of the potential for recurrent operative resections resulting in short bowel syndrome (Fazio 1993).

Laparoscopy has gained wide acceptance in gastrointestinal surgery with potential advantages of faster return to normal activity and diet, reduced hospital stay, reduced postoperative pain, better cosmesis (Duepree 2002, Dunker 1998, Milsom 2001,

Reissman 1996), improved social and sexual interaction (Albaz 2000) and its use is accepted in benign and malignant colorectal diseases. Milsom (Milsom 1993) first reported laparoscopic intestinal resection for patients with CD. Laparoscopic surgery offers additional advantage of smaller abdominal fascial wounds, low incidence of hernias, and decreased rate of adhesive small-bowel obstruction (Albaz 2000) compared with conventional surgery reducing the need for non-disease-related surgical procedures in CD population. If realised in practice, these advantages may lead to reductions in health service utilisation following initial surgery in CD populations, with associated reductions in costs.

There are concerns about missing occult segments of disease and critical proximal strictures due to limited tactile ability, earlier recurrence due to possible reduced immune response induced by laparoscopy, technical difficulty due to fragile inflamed bowel and mesentery and the existence of adhesions, fistulas, and abscesses (Uchikoshi 2004). It is therefore important to evaluate the potential benefits and risks of laparoscopic surgery versus open surgery in patients with small bowel CD (Lowney 2005).

DISCUSSION

This review compared the laparoscopic and open surgical options in the management of small bowel CD. We aimed to perform a subgroup analysis to compare the commonly performed surgical procedures, among CD patients, such as ileocolic resection and anastomosis, small bowel resection and anastomosis, strictureplasty. However, only two randomised controlled trials were published (total of 120 patients) comparing the ileocolic resection and anastomosis in the management of small bowel CD and these were included in the review.

Post operative morbidity and 30-day reoperation rates were considered as primary outcome measures. Less number of patients in the laparoscopic group (2/61) suffered wound infection compared to the open group (9/59) but the difference was not statistically significant (P=0.23). Similarily, there was no significant difference in the incidence of other postoperative complications assessed - postoperative pneumonia, duration of postoperative ileus and urinary tract infections. The incidence of anastomotic leak and intra abdominal abscess rates were comparable between the two groups. The 30-day reoperation rates among the two groups were also comparable.

Surgery for small bowel CD could be technically demanding due to the inflamed bowel, thickened mesentery and associated increased vascularity. Mobilisation of an inflammatory mass adherent to the retroperitoneum including the ureters, gonadal vessels and the remaining small bowel could often be difficult with conventional surgery. Therefore, the duration of surgery is expected to be shorter with open surgery and was reflected in the included studies [P<0.003 in Maartense 2006 and P<0.0001 in

Milsom 2001]. For the same reasons, the amount of intra operative blood loss could be lower with the open surgery. Mean intra operative blood loss was reported in one of the two included studies. It was lesser in the open group (133 +/- 70 ml/ case) compared to laparoscopic group (173 +/- 123 ml / case) although the difference was not statistically significant [P=0.25] (Milsom 2001).

Size of the surgical incision used for laparoscopic surgery is usually smaller compared to open surgery. As a result the patients in the laparoscopic group are expected to experience less post operative pain and decreased need for the opioid analgesics. This in turn should help in early mobilisation after surgery possibly contributing to earlier discharge from the hospital. However, there was no significant difference in the amount of opioids used amongst the two groups in the included studies [P= 0.15 Maartense 2006 and P=0.57 Milsom 2001]. Postoperative hospital stay was lower in the laparoscopic group compared to open group but the difference was not statistically significant [P=0.90].

Conversion rates were similar in both the trials [3 out of 30 in Maartense 2006 and 2 out of 33 in Milsom 2001]. However, it was interesting to note that Milsom et al have performed a diagnostic laparoscopy for all their patients to assess if the candidate was suitable for laparoscopic surgery or otherwise. Conversions were not included in the data analysis. Maartensee et al have not performed diagnostic laparoscopy and have treated conversions on intention-to-treat basis.

There are concerns about missing the sites of disease on laparoscopic surgery and reduced immunity contributing to higher long term disease recurrence rates. However, there was no significant difference in the reoperation rates for disease recurrence.

Laparoscopic surgery for abdominal conditions is known to have associated with lesser incidence of adhesions and the incisional hernias. In the current review the numbers were less in the laparoscopic group (3/57 vs 7/54) but the difference was not statistically significant (P=0.19).

The main drawback of this study was small patient population and it was difficult to make reliable conclusions. Quality of Life (QoL), an important measure of long term outcome, was not reviewed although one of the RCTs (Eshusis 2010) reported similar QoL in both the groups.

To supplement the main systematic review of perioperative outcomes and re-operation rates for disease recurrence following laparoscopic surgery versus open surgery in patients with small bowel CD, we sought to identify economic evaluations which have compared the use of these two alternative surgical techniques in small bowel CD patients. Systematic supplementary searches of the NHS Economic Evaluation Database and the Health Economic Evaluations Database identified six relevant economic evaluations. A cost-effectiveness analysis (cost consequences) conducted alongside one

of the multi-centre randomised controlled trials included in this review compared clinical and health-related quality of life outcomes and perioperative costs associated with laparoscopic-assisted versus open ileocolic resection in CD patients (Maartense 2006). The economic analysis appears to have adopted a single provider (hospital) perspective and it adopts a 3-month time horizon including and following initial surgery. In common with the findings of the review of perioperative outcomes and re-operation rates, the authors found no clear difference in clinical or health-related quality of life outcomes between laparoscopic-assisted and open resection but did find lower total direct hospital costs per patient in the laparoscopic group compared with the open group.

A cost-effectiveness analysis (cost consequences) conducted alongside a single empirical study (a single-centre, prospective non-randomised study) compared postoperative clinical outcomes, return to work and perioperative costs up to discharge associated with laparoscopic-assisted versus open ileocolic resection in CD patients (Dupree 2002). The economic analysis appears to have adopted a single provider (hospital) perspective. It found shorter post-operative recovery time, faster return to work and lower total direct hospital costs per patient in the laparoscopic-assisted group compared with the open group.

A cost-effectiveness analysis (cost consequences) conducted alongside a single empirical study (a single-centre, retrospective, non-randomised study, with patients in the two groups matched for age, gender, diagnosis, type of resection and date of operation), compared postoperative clinical outcomes and perioperative costs associated with laparoscopic versus open ileocolic resection in CD patients (Young-Fadok 2001. The economic analysis appears to have adopted a societal perspective. It found improved postoperative clinical outcomes and lower direct (perioperative) health care and indirect costs per patient in the laparoscopic group compared with the open group.

A cost-effectiveness analysis (cost consequences) conducted alongside a single empirical study (single centre, prospective non-randomised study) compared perioperative clinical outcomes and cost of hospital admission associated with laparoscopic versus open ileocolic resection in patients with inflammatory bowel disease, 90% of whom had CD (Msika 2001)..The economic analysis appears to have adopted a single provider (hospital) perspective. It found lower cost of hospital admission per patient in the laparoscopic group compared with the open group.

A cost effectiveness analysis (cost consequences) conducted using a single centre, non-randomised, retrospective analysis of a hospital database) compared clinical outcomes and hospital charges associated with laparoscopic-assisted versus open ileocolic resection in CD patients (Shore 2003). The economic analysis appears to have adopted a single provider (hospital) perspective. Mean follow-up (time horizon) was 17.2 months

(laparoscopic group) and 18.7 months (open group) It found lower hospital charges per patient in the laparoscopic-assisted group compared with the open group.

A cost analysis (prospective cohort study) compared direct perioperative health care costs and indirect costs (lost working days during sick leave) associated with laparoscopic-assisted versus open ileocolic resection in CD patients (Scarpa 2009). The economic analysis appears to have adopted a societal perspective. It found lower costs per patient for hospital stay in the laparoscopic-assisted group compared with the open group, but no difference in total costs (where total costs combine direct perioperative health care costs with costs associated with lost working days during sick leave).

We did not subject theses six identified economic evaluations to critical appraisal and we do not attempt to draw any firm or general conclusions regarding the relative costs or efficiency of the surgical techniques compared. Also, with the exception of Maartense 2006, all the economic evaluations we identified were conducted within the framework of single, empirical studies with non-randomised study designs. The body of available economic evidence is therefore likely to be at high risk of bias and results should be viewed with caution. Additionally, the majority of those economic evaluations we identified assessed (short-term) perioperative costs (and outcomes) only, were conducted in single centres, and adopted a limited single provider perspective.

Taking into account these limitations, there was consistency between economic evaluations in the finding that short-term direct health care costs were, on average, lower amongst CD patients who underwent laparoscopic-assisted or laparoscopic surgery compared with those who underwent open surgery. When considered alongside the principal finding from our main review of intervention effects that there is no clear difference in perioperative outcomes and re-operation rates for disease recurrence between laparoscopic-assisted or laparoscopic and open techniques, the available economic evidence indicates that, from an economic perspective, laparoscopic-assisted or laparoscopic ileocolic resection may be promising techniques, as comparably safe and lower cost alternatives to open surgery, in CD patients. End users of this review will need to assess the extent to which methods and results of identified economic evaluations may be applicable (or transferable) to their own setting.

Wildschut 2011

DISCUSSION

Second trimester medical abortion regimens have evolved greatly over the past 20 years with increasing availability of prostaglandin analogues and anti-progesterone agents such as mifepristone. Older regimens such as instillation of hypertonic saline or prostaglandin F2 although effective in provoking abortion, were associated with higher rates of serious adverse events than are modern methods (Bygdeman and Gemzell-Danielsson 2008).

Randomised comparisons included in this review demonstrate that misoprostol is the prostaglandin analogue of choice: it is as effective or more effective than other studied prostaglandins and has the preferable characteristics of heat stability and multiple administrative routes. However, in settings where prostaglandins are not available for second trimestermedical abortion, extra-amniotic instillation of ethacridine lactate may be an alternative (Comparisons 23, 24) (Hou 2010). However, limited information is available percentage of women needing a surgical intervention for incomplete abortion and the safety outcomes of ethacridine lactate, given the small number of subjects studied. When using extraamniotic instillation of drugs, the catheter tends to be expelled as the cervix dilates, before the abortion process is self-sustaining. For this reason, supplementary infusions of oxytocin are commonly used (Kelekci 2006; WHO technical report series) which also increases the associated costs. Furthermore, intra-amniotic injection of drugs is potentially dangerous as accidental injection into maternal tissue or placenta can result in local tissue damage or harmful absorption into the maternal circulation (WHO technical report series). For this reason, the drugs should only be given by skilled operators. Intra-amniotic injection of drugs may also induce infection into the amniotic cavity (WHO technical report series).

Misoprostol when used alone is an effective inductive agent; however, it appears more efficient when combined with mifepristone, although the evidence from randomised trials is limited. In fact, there is only one relatively small randomised study (Kapp 2007) comparing the effect of misoprostol + mifepristone with misoprostol only (Comparison 2). This study demonstrated that the addition of mifepristone in second trimester abortion reduces the induction to abortion interval from 18 hours (95% CI 1 to 22) to 10 hours (95% CI 8 to12), while the occurrence of side-effects in both groups was similar. Indirect evidence, however, suggests a beneficial effect of adding mifepristone to prostaglandin tablets or gel since the induction-to-abortion interval is generally shorter in regimens using mifepristone + prostaglandins (Comparisons 1, 3, 4, 5 and 7) than those using prostaglandins alone (Comparisons 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 and 19). Additionally, mifepristone is known to potentiate the uterine effect of misoprostol and is superior to misoprostol alone in first trimester abortion.

Misoprostol may be administered by different routes, the oral route being the least effective (Comparisons 3, 4 and 5). For regimens using misoprostol, vaginal dosing appears to be the most efficient when compared to both oral and sublingual regimens. Among multiparous women undergoing medical abortion with misoprostol alone, sublingual administration appears equally effective as vaginal administration. No study of second trimester medical abortion has compared vaginal with buccal administration of misoprostol.

The optimal dose of vaginally administered misoprostol is difficult to ascertain since there are no randomised studies comparing various dosing schemes for vaginal administration. Four randomised clinical trials showed that the induction to abortion interval with 3-hourly vaginal administration of prostaglandins was significantly shorter than 6-hourly administration without significant increase in side-effects (Comparisons 15 and 16).

There is insufficient data to make any gestational, age-specific recommendations on the dosage and regimen for abortion. Since the uterus becomes more sensitive to prostaglandins with increasing gestational age, reducing the dosage or frequency of administration should be considered at later gestational ages (Ho 2007). The age range considered in this review includes 12 through 28 weeks of gestation. Overall, from the design of the included studies, there is no indication for confounding by gestational age.

Other considerations for second trimester medical abortion regimens which could not be addressed in this review include the effect on the abortion process of the use of pre-procedure feticide to avoid the occurrence of a fetus with signs of life at abortion, and therapeutic strategies for women who have not aborted after 24 hours of treatment.

There are considerable differences in practices regarding the management of the placenta following the expulsion of the fetus. We considered surgical evacuation any procedure where an instrument was introduced into the uterine cavity. Indications for surgical evacuation include the removal of retained products of the placenta and heavy vaginal bleeding, where reported. Fewer women required surgical evacuation when misoprostol was administrated vaginally when compared to women having mid-trimester abortion by intra-amniotic instillation of PGF2 (OR 0.52, 95% CI 0.31 to 0.87) (Comparison 9). Apart from the latter finding, there were no statistically significant differences in reported frequencies of surgical removal of the placenta among women undergoing misoprostol-induced abortions when compared to other regimens.

Diarrhoea is the most common adverse reaction that has been reported consistently with misoprostol, but it is usually mild and self limiting. Nausea and vomiting may also occur and generally resolves in two to six hours (Tang 2007). Uterine rupture is a rare but serious complication of abortion in the second trimester of pregnancy, especially in women with a previous uterine scar (Berghella 2009).Uterine rupture is uncommon and did not occur during any of the included trials; thus, its relative risk with differing

medical regimens are not informed by this review.

Summary of main results
Thirty-six randomised controlled trials were included in the review. The included studies addressed the various agents for pregnancy termination and methods of administration which were grouped into 28 comparisons. When used alone, misoprostol is an effective inductive agent, though it appears to bemore effective in combination with mifepristone.

Misoprostol is preferably administered vaginally, although among multiparous women sublingual administration appears equally effective. The optimal dose of vaginally administered misoprostol could not be determined, as no randomised studies could be identified. Low doses of misoprostol are associated with fewer side-effects, while moderate doses are more efficient in completing abortion. Four randomised controlled trials showed that the induction to abortion interval with 3-hourly vaginal administration of prostaglandins is significantly shorter than 6-hourly administration without a significant increase in side-effects.

Many studies reported the need for surgical evacuation in a considerable number of women undergoing mid-trimester termination. Indications for surgical evacuation include the removal of retained products of the placenta and heavy vaginal bleeding. Fewer women required surgical evacuation when misoprostol was administrated vaginally when compared with those having intra-amniotic instillation of PGF2a . Apart from the latter finding, there were no statistically significant differences in reported frequencies of surgical removal of the placenta among women undergoing misoprostol induced abortions when compared to other regimens. Diarrhoea was more common among women having misoprostol when compared to other agents. However, diarrhoea is reportedly mild and self limiting.

Overall completeness and applicability of evidence
The results of this review fit well into the current practices of midtrimester termination of pregnancy.

Quality of the evidence
All randomised controlled trials, most of these being unblinded. Given the heterogeneity of the some studies included in the review, the internal validity of the findings is limited.

Potential biases in the review process
None.

Agreements and disagreements with other studies or reviews
Agree with recent Society for Family Planning Guidelines, in press.

Economic evidence
To supplement the main systematic review of the efficacy and side-effects of medical

regimens for second trimester medical abortion, we sought to identify relevant economic evaluations of medical regimens compared in this review. Systematic supplementary searches of the NHS Economic Evaluation Database and the Health Economic Evaluations Database identified one relevant economic evaluation. A cost effectiveness analysis (cost-consequences) conducted within the framework of a single-centre randomised controlled trial included in this review (Ngai 2000) compared the clinical outcomes and drug costs associated with vaginal (200 µg every 3 hours up to five doses) versus oral (400 µg every 3 hours up to five doses) administration of misoprostol, combined with oral mifepristone (200 mg), in termination of second trimester pregnancy (Comparison 3) in Hong Kong. The economic analysis identified higher (four-fold increase) drug costs associated with use of oral misoprostol compared with vaginal misoprostol - $9.68 compared with $2.10 per patient (HKD - price year not stated). The apparent shortage of relevant economic evaluations indicates that economic evidence regarding medical regimens for second trimester medical abortion is currently lacking.

Komossa 2011

BACKGROUND

Description of the condition

Schizophrenia is usually a chronic and disabling psychiatric disorder which afflicts approximately one per cent of the population world-wide with little gender differences. The annual incidence of schizophrenia averages 15 per 100,000, the point prevalence averages approximately 4.5 per population of 1000, and the risk of developing the illness over one's lifetime averages 0.7%. (Tandon 2008). Its typical manifestations are positive symptoms such as fixed, false beliefs (delusions) and perceptions without cause (hallucinations), negative symptoms such as apathy and lack of drive, disorganisation of behaviour and thought, and catatonic symptoms such as mannerisms and bizarre posturing (Carpenter 1994). The degree of suffering and disability is considerable, with 80%-90% not working (Marvaha 2004) and up to 10% dying (Tsuang 1978). In the age group of 15-44 years, schizophrenia is among the top 10 leading causes of disease-related disability in the world (WHO 2001).

The global economic burden of schizophrenia is high and the costs-of illness are wide-ranging. A 2004 review of international cost-of-illness studies indicated that the impact of schizophrenia on health care budgets is typically between 1.5% and 3% of total national health care expenditures and that costs fall not only on the healthcare sector but also on other parts of the public sector, patients, families, and wider society (Knapp 2004). An earlier review of international cost-of-illness studies indicated that annual costs of schizophrenia ranged from $139 million in Australia (1994 USD) to $65.2 billion in the United States (1994 USD) (Genduso 1997).

Description of the intervention

Conventional antipsychotic drugs such as chlorpromazine and haloperidol have traditionally been used as first-line antipsychotics **f**or people with schizophrenia (Kane 1993). The reintroduction of clozapine in the United States of America and a finding that clozapine was more efficacious and associated with fewer movement disorders than chlorpromazine (Kane 1988) has boosted the development of so-called "atypical" or new (second) generation antipsychotics (SGA).There is no good definition of what an "atypical" or SGA is, but they were initially said to differ from typical antipsychotics in that they do not cause movement disorders (catalepsy) in rats at clinically effective doses (Arnt 1998). The terms "new" or "second generation" antipsychotics are not much better, because clozapine is a very old drug. According to treatment guidelines (APA 2004; Gaebel 2006) SGAs include drugs such as amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, sertindole, ziprasidone and zotepine, although it is unclear whether some old and cheap compounds such as sulpiride or perazine have similar properties (Möller 2000). The SGAs raised major hopes of superior effects in a number of areas such as compliance, cognitive functioning, negative symptoms,

movement disorders, quality of life and the treatment of refractory people with schizophrenia.

Indeed, evidence from international reviews of cost-of-illness studies indicates the potential economic benefits associated with such effects; inpatient care has been identified as a key driver of direct healthcare costs, which suggests that relapse prevention, including through prescription of more effective and acceptable antipsychotics, can play an important role in reducing overall health care costs (Knapp 2004, Genduso 1997). In one US study, the national annual direct cost of hospital admissions for relapsing schizophrenia patients was estimated at $2.3 billion (1993 USD), with loss of neuroleptic efficacy accounting for approximately 63 per cent of rehospitalisation costs and neuroleptic noncompliance for about 37 per cent (Weiden 1995).

How the intervention might work

Risperidone has high affinity to 5-HT2 and D2 receptors; it also binds to a1 receptors and with lower affinity to H1 and a2 receptors. It was developed following the observation that a selective serotonin receptor blocker (ritanserin) produced a beneficial effect when combined with conventional neuroleptics (Gupta 1994; Curtis 1995). Risperidone is described to have no affinity to cholinergic receptors. Although being a potential D2 antagonist it causes less motor retardation and cataleptic symptoms than typical antipsychotics (Janssen-Cilag 2005).

Why it is important to do this review

The debate as to how far the SGA improve these outcomes compared to conventional antipsychotics continues (Duggan 2005; El-Sayeh 2006) and the results from recent studies are sobering (Jones 2006; Lieberman 2005). Nevertheless, in some parts of the world, especially in the highly industrialised countries, SGA have become the mainstay of treatment. The SGAs also differ in terms of their costs: while amisulpride and risperidone are already generic in many countries in 2009, aripiprazole, olanzapine, quetiapine, sertindole and ziprasidone are still not. Therefore the question as to whether they differ from each other in their clinical effects becomes increasingly important. In this review we aim to summarise evidence from randomised controlled trials that compared risperidone with other SGAs.

DISCUSSION

Summary of main results

1. General

In the last years the number of randomised risperidone trials has dramatically increased. A previous Cochrane review comparing risperidone with other SGA drugs included only nine RCTs (Gilbody 2000). The current review includes 45 RCTs, although

we had more stringent inclusion criteria and excluded open RCTs. Nevertheless, many problems that were identified by the previous review have not been solved:

The number of participants leaving schizophrenia trials prematurely remain high (Wahlbeck 2001). The overall attrition of 47% in the included studies is a threat to the validity of the findings. Adverse events were often only reported if they had a frequency of 5%/10% or greater. This procedure results in underreporting of rare but important adverse effects. We suggest to abandon the >5%/10%frequency rule for reporting of adverse effects and suggest that all adverse events should be reported instead, for example as online supplements that are nowadays made available by most journals.

Most trials provided data on leaving the studies early and overall efficacy. Outcomes that are possibly more important for daily life such as general functioning or satisfaction with treatment are rarely presented. Authors keep using different criteria for 'response to treatment' making comparisons difficult, although validated suggestions for the presentation of response to treatment are available (Leucht 2005a; Leucht 2005b; Van Os 2006).

More than half of the 45 included trials were categorised as 'short term' studies and only eight were 'long-term' studies with a length of more than 26 weeks. Schizophrenia is a chronic, often life-long disorder, making more long-term studies necessary.

60% of the studies were sponsored by pharmaceutical companies producing either risperidone or its comparator drugs, whereas only 31% of the studies had a neutral sponsor (the sponsor of the remaining RCTs remained unclear). Due to the inevitable conflict of interest, industry sponsorship is a concern (Heres 2006).

Finally, most studies compared risperidone with clozapine, olanzapine and quetiapine. Fewer RCTs comparing risperidone with amisulpride, aripiprazole, sertindole and ziprasidone are available, and comparisons with zotepine are completely missing.

2. Comparison 1. Risperidone versus amisulpride

2.1 Leaving the studies early

There were no significant differences in the number of participants leaving the studies early due to any reason, due to adverse events or due to inefficacy of treatment. These results suggest a similar overall acceptability, tolerability and efficacy of risperidone and amisulpride. Nevertheless, four studies with 622 participants do not provide a firm basis for such a conclusion. Furthermore, although the overall rate of participants leaving the studies early of 33.2% was lower than that of some other comparisons, it was still considerable.

2.2 Efficacy outcomes (global state, overall and specific mental state)

There was no clear efficacy difference between risperidone and amisulpride. There was a significant superiority of amisulpride in terms of 50% BPRS reduction. However, this

result was based on only one trial and may have well occurred by chance alone, given the high number of statistical tests applied (Sechter 2002). Furthermore, the same trial did not find any difference in the mean values at endpoint of the BPRS.

2.3 General functioning

A single study using the SOFAS scale reported on social functioning and found no difference between risperidone and amisulpride. Pragmatic studies that are conducted in situations that are more similar to routine care are needed to address this important outcome.

2.4 Adverse effects

There were some data on extrapyramidal side effects, cardiac effects, prolactin associated side effects, sedation, seizures and death. Besides the reporting on sexual dysfunction which indicated a benefit for amisulpride, the only adverse event showing a significant difference was weight gain which was 1kg more in the risperidone group. This difference was found in short- to medium-term studies. It may well be that the difference would be more pronounced in the long term, but longer studies are needed to verify this assumption. Nevertheless, if metabolic issues are a concern, amisulpride may be a better choice than risperidone.

3. Comparison 2. Risperidone versus aripiprazole

3.1 Leaving the studies early

Again, the number of participants leaving the two studies early was considerable (34.4%).There was no significant difference between both compounds, suggesting that their acceptability is similar, but two included studies - both sponsored by the manufacturers of aripiprazole - are no firm basis for any conclusion.

3.2 Efficacy outcomes (global state, overall and specific mental state)

There were no statistically significant differences in global state, general mental state, positive and negative symptoms. The currently available small evidence base does thus not suggest a difference in efficacy between both compounds. Nevertheless, ”no evidence of effect does not mean evidence of no effect“ (Tarnow-Mordi 1999).

3.3 Adverse effects

Limited data were available on extrapyramidal side effects, cardiac effects, cholesterol, glucose, prolactin increase, prolactin associated side effects and weight gain. There was a significant benefit for aripiprazole in terms of dystonia, QTc abnormalities, prolactin increase and cholesterol levels, whereas tremor was less frequent in the risperidone group. Overall risperidone´ s tolerability profile may be somewhat worse than that of aripiprazole, but these results are based on very limited data. Any conclusion would be premature.

4. Comparison 3. Risperidone versus clozapine

4.1 Leaving the studies early

The 11 included studies showed a considerable overall attrition of 33.4%. Although this attrition was not as high as in some other comparisons of this review, it nevertheless limits the interpretation of all results beyond the outcome of leaving the studies early.

A similar number of participants in the risperidone and the clozapine groups left the studies early due to any reason, suggesting a comparable overall acceptability of both compounds. Nevertheless, there were significant differences in the reasons why participants left the studies.

Adverse events were a greater problem in the clozapine group. Clozapine is associated with a number of serious and partly dangerous adverse effects such agranulocytosis, seizures, sedation or weight gain (see 4.4 below), which may explain risperidone's superiority in this regard.

Inefficacy of treatment led more frequently to leaving the studies early in the risperidone group. This suggests a certain efficacy superiority of clozapine. Indeed, clozapine was associated with a somewhat more pronounced reduction of positive symptoms than risperidone, although the difference was not robust (see 4.2 below).

4.2 Efficacy outcomes (global state, overall and specific mental state)

The only significant difference between risperidone and clozapine was a superiority of the latter in terms of positive symptoms. Even this difference was not robust, because when two studies with possibly skewed data were excluded it was no longer statistically significant.

This failure to find clozapine superior was surprising, because clozapine is generally considered to be the most efficacious antipsychotic drug available. This superiority has recently been confirmed by the industry independent studies CATIE II (McEvoy 2006) and CUtLASS (Lewis 2006) which could not be included here. The clozapine group of CATIE II was a non-blinded study arm and CUtLASS compared clozapine with a number of second generation antipsychotics as a group.

One reason for the failure to find a consistent superiority of clozapine may be that efficacy was addressed in different ways (e.g. different scales or different definitions of response to treatment), making a summation difficult. Indeed at most six out of 11 studies could be combined in a meta-analysis, and frequently the results were even based on only one RCT.

Another possible explanation may be relatively low clozapine doses. The mean doses in two pivotal studies demonstrating clozapine's superiority to first-generation antipsychotic drugs were 600mg/day (Kane 1988) and 523mg/day (Rosenheck 1997). A randomised, blinded dose finding study found that a clozapine dose of 600mg/day was more efficacious than lower doses (Simpson 1999). In contrast, of the 11 trials

included in this review only two studies had mean clozapine doses higher than 500mg/ day (Volavka 2002: 526mg/day; Azorin 2001: 642 mg/day), and indeed the latter study found a superiority of clozapine. Several trials limited the upper clozapine dose range to 400mg/day. Nevertheless, a definitive, industry independent trial with sufficient clozapine doses is necessary to establish the relative efficacy of clozapine and risperidone.

4.3 General functioning

Only a very small study reported on general and social functioning, but found no significant difference between groups. From a more global public health perspective, but also for people with schizophrenia, it may be more important to know whether a drug improves functioning in the community than whether it reduces symptoms. It is therefore disappointing that so few data on these important outcomes were available.

4.4 Adverse effects

Very few data on extrapyramidal side effects, cardiac effects, change in cholesterol level, death, prolactin increase and associated side effects, sedation, seizures, and low white blood cell count were available. At most five (sedation, white blood cell count) to six (use of anti-parkinson medication) out of 11 included studies could be combined in a meta-analysis. This may well reflect selective reporting and limits the conclusions.

Nevertheless, risperidone was associated with clearly more use of antiparkinson medication than clozapine. Use of antiparkinson medication is a useful proxy measure of movement disorders. One out of six people treated with risperidone instead of clozapine suffered from these very unpleasant adverse events which are well visible and can therefore contribute to the stigma associated with schizophrenia.

Risperidone also produced more prolactin increase than clozapine. This result was based on only two RCTs, but prolactin increase is a well-known adverse event of risperidone. The long-term consequences can be osteoporosis and sexual side effects, although the latter could not be demonstrated in this review, at least partly because the individual studies presented so few data.

Conversely clozapine was associated with more seizures, sedation and weight gain. One out of 14 participants treated with clozapine instead of risperidone had a seizure. This is a considerable and clinically important difference, because seizures are dangerous adverse events. Clozapine is well known for its sedating effects. Many people taking antipsychotic drugs do not like the sedation associated in varying degrees with these compounds, but sometimes sedation is only transient. The weight gain produced by clozapine is a major concern, because in the long term it can lead to diabetes and cardiovascular diseases such as myocardial infarction or stroke. It is reassuring that - despite the limited data available - the review was able to document some of the expected differences in tolerability between risperidone and clozapine. Clinicians and

people with schizophrenia may use the results in their choice of drug.

5. Comparison 4. Risperidone versus olanzapine

5.1 Leaving the studies early
Risperidone and olanzapine have been compared in a relatively large number of 23 blinded RCTs and 3207 participants. Nevertheless, the high overall rate of participants leaving the studies early (52%) is a source of concern. The field must urgently find ways to decrease the amount of attrition in schizophrenia trials, because the typically high discontinuation rates make the validity of the results questionable.

Risperidone may be a somewhat less acceptable treatment than olanzapine for people with schizophrenia, because more participants in the risperidone group left the studies early due to any reason. In addition, more risperidone treated participants left the studies early due to inefficacy of treatment. This may reflect a somewhat better efficacy of olanzapine which is also supported by a stronger improvement of the participants' general mental state (see below). Leaving the studies early due to adverse events showed no difference between groups suggesting a similar overall tolerability of risperidone and olanzapine

5.2 Efficacy outcomes (global state, overall and specific mental state)
Most data were available for the general mental state (PANSS total score, 15 RCTs) and positive and negative symptoms of schizophrenia (PANSS positive and negative subscore, 13 RCTs). Olanzapine was slightly superior in the improvement of the general mental state, but not superior for specific symptoms of schizophrenia. The difference was numerically very small (two points difference on the PANSS total score) and of questionable clinical importance. Only three studies reported on responder rates defined as 'at least 50% reduction of the PANSS total score' and found a marginal but statistically significant difference in favour of olanzapine (RR 1.09). A number needed to harm could not be calculated, because the risk difference was not significant. Most other efficacy-related outcomes were based on very small numbers and showed equivocal results.

5.3 Quality of life
The results suggested a better quality of life of participants treated with olanzapine compared to risperidone. Since only two studies provided data on this outcome, any recommendation for practice would be premature.

5.4 Cognitive functioning
Only two studies compared the cognitive effects of risperidone and olanzapine and found no significant difference between groups.

5.5 Service use
In three trials a similar number of participants in the risperidone and olanzapine groups

had to be rehospitalised. This lack of a difference suggests a similar efficacy of both compounds. Or possible efficacy differences are so small that they do not translate in more global outcomes such as rehospitalisation.

5.6 Adverse effects

The adverse effects that occurred in a statistically significantly different frequency can be grouped in three categories. Olanzapine was associated with more weight gain and associated metabolic problems such as cholesterol and glucose increase. Therefore, risperidone might be a more appropriate treatment for people at risk to develop a metabolic syndrome, overweight people, individuals suffering from diabetes or those with high cholesterol levels.

Risperidone produced some extrapyramidal side effects more frequently than olanzapine. Namely, the participants in the risperidone group used more antiparkinson medication and suffered more frequently from akathisia and parkinsonism. Although the number needed to treat for use of antiparkinson medication was relatively high (NNT 17), movement disorders are very unpleasant side effects and should be avoided.

Risperidone was also associated with clearly more prolactin increase and related sexual dysfunctions such as abnormal ejaculation in men and amenorrhea in women. Clinicians and people with schizophrenia may consider these different tolerability profiles of both compounds in their drug choice.

6. Comparison 5. Risperidone versus quetiapine

6.1 Leaving the studies early

We included 11 studies with 3770 participants in this comparison. This could be a reasonable basis for the examination of the relative effects of risperidone and quetiapine, but the overall discontinuation rate was high (56.7%). Such high attrition limits the interpretation of any other results beyond the outcome leaving the studies early. If more than 50% of the data must be estimated by statistical modelling, the validity of the findings is called into question. Nevertheless, there was no clear difference in the number of participants leaving the studies early due to any reason or due to adverse events, suggesting a similar overall acceptability and tolerability of risperidone and quetiapine. Only the outcome leaving the studies early due to inefficacy tended to favour risperidone, which is consistent with a certain efficacy superiority of risperidone (see 6.2 below).

6.2 Efficacy outcomes (global state, overall and specific mental state)

The only statistically significant differences in efficacy were found for the general mental state and positive symptoms. Risperidone was more efficacious than quetiapine in these aspects of psychopathology. Nevertheless, the differences were small (e.g. only 3 points on the PANSS total score). The clinical relevance of this difference is difficult to interpret. Unfortunately, dichotomous data on response to treatment, which can be

interpreted more intuitively, were rarely indicated. Only four studies (less than half of those available for the PANSS total score) showed a trend in favour of risperidone in terms of 'no important improvement of the participants' global state' (P = 0.06) which did not reach the conventional 5% level of statistical significance.

6.3 Adverse effects

Adverse effects were available for at least one adverse effect, cardiac effects, cholesterol increase, changes in serum glucose, increase of prolactin level and associated side effects, death, extrapyramidal side-effects, sedation, weight gain and white blood cell count. Among these, risperidone was worse than quetiapine in various measures of extrapyramidal side effects and prolactin associated effects. Although the differences were not very large (e.g. among 20 participants treated with risperidone instead of quetiapine one needed antiparkinson medication) extrapyramidal side effects are very unpleasant adverse events which should be avoided. Prolactin increase can lead to sexual side effects and indeed the frequency of amenorrhea and galactorrhea was approximately two times higher in the risperidone group.

Conversely quetiapine was associated with more sedation and cholesterol increase than risperidone. The long-term consequences of the latter adverse event can be cardiovascular problems such as myocardial infarction or stroke.

These differences in the side effect profile and the slightly better efficacy of risperidone may be weighed in drug choice.

7. Comparison 6. Risperidone versus sertindole

Again only two studies could be included in this comparison and one of the studies (Kane 2005) has to date only been published as a conference poster presenting limited information. This evidence base is too limited to draw firm conclusions.

7.1 Leaving the studies early

Although the number of participants leaving the studies early due to any reason was considerable (33.7%), there was no significant difference between sertindole and risperidone, suggesting a similar overall acceptability of treatment. Specific reasons for leaving the studies early (adverse events, inefficacy of treatment) did not show a difference between both compounds either.

7.2 Efficacy outcomes (global state, overall and specific mental state)

There was no clear difference in efficacy based on CGI, PANSS totals score, PANSS positive and negative subscore. Nevertheless, the results on the general mental state as measured by the PANSS total score were heterogeneous. One study suggested that in people with treatment-resistant schizophrenia, risperidone may be somewhat more efficacious (Kane 2005), while in the other study without this criterion, no difference was found (Azorin 2006). Any interpretation is certainly limited by the small number of

included trials and participants. Replications are needed.

7.3 General functioning

Only one short-term study provided data on general functioning and showed no difference between groups. We believe that long-term, real world, pragmatic studies are needed to examine this important outcome.

7.4 Adverse effects

There were some data on extrapyramidal symptoms, cardiac effects, cholesterol, glucose, sedation, sexual dysfunction, suicide and weight gain.

These limited data suggest that akathisia and parkinsonism may occur more frequently under treatment with risperidone than with sertindole. However, relatively high risperidone dose ranges of 4-10 mg/day and 4-12 mg/day in the two included studies must be taken into account. It is well known that the EPS risk of risperidone is dose related and lower doses (e.g. 2-8mg/day) may produce similar efficacy, but are better tolerated (Marder 1994).

Conversely cardiac effects (QTc prolongation), male sexual dysfunction and weight change indicated a benefit for risperidone. These differences in tolerability may be considered in drug choice. Due to the known effects of sertindole on the QTc interval, the drug cannot be recommended for people with schizophrenia and cardiac problems. The long-term consequences of weight gain such as diabetes and cardiovascular disease can be dramatic.

8. Comparison 7. Risperidone versus ziprasidone

Data based on three studies were available for this comparison. Similar to the comparisons with olanzapine and quetiapine, a very high overall attrition of 63.1% clearly limits the interpretation of any findings beyond the outcome leaving the study early.

8.1 Leaving the studies early

As fewer participants in the risperidone group than in the ziprasidone group left the studies prematurely, risperidone may be more acceptable for people with schizophrenia. As there were no significant differences in specific reasons (adverse events of inefficacy of treatment) for study discontinuation, the reason for this better acceptability is unclear.

8.2 Efficacy outcomes (global state, overall and specific mental state)

A statistically significant, but numerically small benefit (4 points difference on the PANSS total score) for risperidone was present in general mental state and in positive symptoms. Although the small number of included trials and the high drop-out rates limit the validity of this finding, risperidone maybe somewhat more efficacious for the

positive symptoms of schizophrenia than ziprasidone. Whether the numerically small difference is clinically important is again difficult to say. Unfortunately dichotomous data on response to treatment which can be more intuitively understood were only reported by a single study which did not find a significant difference. It cannot be excluded that selective reporting played a role.

8.3 Adverse effects

Ziprasidone was more tolerable than risperidone concerning a number of adverse events: certain extrapyramidal side effects, glucose levels, cholesterol increase, prolactin increase, and weight gain.

In treatment decisions this better tolerability profile of ziprasidone needs to be weighted with the somewhat lower efficacy, always keeping in mind the small amount of available data.

9. Summary

The review currently includes 45 at least single blind studies and 7760 participants. The number of RCTs available for each comparison varied: four studies compared risperidone with amisulpride, two with aripiprazole, 11 with clozapine, 23 with olanzapine, 11 with quetiapine, two with sertindole, three with ziprasidone and none with zotepine. Attrition from these studies was high (46.9%). This high attrition makes the interpretation of the results problematic, because half of the results must be estimated by statistical modelling. Furthermore, 60% were industry sponsored, which can be a source of bias.

Risperidone was slightly less acceptable than olanzapine, and slightly more acceptable than ziprasidone in terms of leaving the studies early due to any reason. The results of all other comparisons were equivocal. There were also only few differences in efficacyrelated outcome; risperidone may be somewhat more efficacious than quetiapine and ziprasidone, but slightly less efficacious than olanzapine and clozapine. Whether the differences are clinically meaningful is difficult to say, because most studies reported the mean scores of rating scales, whereas only a few reported more intuitive data on response to treatment and used different definitions for this.

It was the best documented tolerability difference of the review that risperidone produced somewhat more extrapyramidal side effects than a number of other SGA drugs (all except for amisulpride and aripiprazole compared to which only a few RCTs were available). Risperidone also increased prolactin levels clearly more than all comparators, except for amisulpride and sertindole for which no data were available.

Other differences in adverse effects were less well documented, but risperidone may well produce more weight gain and/or associated metabolic problems than amisulpride, aripiprazole and ziprasidone, but less than clozapine, olanzapine,

quetiapine and sertindole. It may be less sedating than clozapine and quetiapine, lengthen the QTc interval less than sertindole, produce fewer seizures than clozapine and less sexual dysfunction in men than sertindole.

Overall completeness and applicability of evidence

The amount of RCTs comparing risperidone with the other SGA drugs varied substantially. A high number of studies compared risperidone with olanzapine with risperidone (N = 23). A reasonable amount of trials comparing olanzapine with clozapine (N = 11) and quetiapine (N = 11) was available. In contrast, few trials compared olanzapine with amisulpride (N = 4), aripiprazole (N = 2), sertindole (N = 2) and ziprasidone (N = 3). We did not identify any RCT comparing risperidone with zotepine. Therefore the evidence is incomplete.

Furthermore, it is also obvious that most of the studies reported on leaving the studies early due to any reason and overall symptoms of schizophrenia. All other outcomes were usually based on much smaller numbers. Very little information is available on general functioning, satisfaction with care or cognition. These outcomes may be more important for people suffering from schizophrenia than the improvement of symptoms. Only three included studies reported on service use, although such data would be crucial for policy makers.

Most of the included studies had tight inclusion criteria limiting external validity. Further effectiveness studies are needed.

Quality of the evidence

A major threat for the quality of the evidence is the high overall attrition of 47% in the studies. It is questionable whether even a sophisticated statistical method can account for such a high percentage of participants leaving the studies before their end. Most studies used the last observation carried forward method which is based on the assumption that a participant leaving a study early would not have changed if he had stayed in the study. This assumption can obviously be wrong.

All included studies were stated to be randomised and all but seven studies were double-blind. The remaining seven trials described blinded raters. Nevertheless, the randomisation and blinding methods were rarely described. The study authors did also not make attempts to verify whether blinding was successful.

The majority of the trials fell in the short-term category, which is problematic in a chronic disease such as schizophrenia. All these factors limit the overall quality of the evidence.

Potential biases in the review process

We are not aware of obvious flaws in our review process. Nevertheless, we admit that we present only a selection of outcomes. Although these outcomes were defined a priori

in the protocols and although we think that we made a meaningful selection, other people may have different opinions and differences in other outcomes may have been missed.

Agreements and disagreements with other studies or reviews

Many new RCTs have compared risperidone with other SGA drugs since the publication of a previous Cochrane review on the same topic (Gilbody 2000). Gilbody 2000 included only nine RCTs which compared risperidone with clozapine, olanzapine and amisulpride. Due to this large difference in sample size the reviews are hardly comparable. Nevertheless, as in our review risperidone was overall as acceptable as clozapine for people with schizophrenia (leaving the study early due to any reason), but slightly less acceptable than olanzapine. Efficacy data tended to favour clozapine and olanzapine, but statistically significant effects were rare which is not surprising, because even in the current much larger review the differences were small. Risperidone also produced more extrapyramidal side effects but less weight gain than olanzapine, while very few side effect data compared to clozapine were available. As in the current review there were no major differences between risperidone and amisulpride and the evidence base has grown only slightly (from one to four RCTs).

Another more recent review specifically compared risperidone with olanzapine (Jayaram2006). Again, more participants in the risperidone group left the studies early due to any reason, but there were no clear differences in the efficacy of both compounds. Risperidone produced more extrapyramidal side effects, but less weight gain and associated metabolic effects than olanzapine. Overall, we believe that many findings of the previous reviews are compatible with the current report. Therefore, the evidence has become more robust, although still insufficient in quality, over time.

Economic evidence

To supplement the main systematic review of effects, we sought to identify economic evaluations which have compared risperidone with other atypical antipsychotics for people with schizophrenia or other schizophrenia-like psychoses. Systematic supplementary searches of the NHS Economic Evaluation Database and the Health Economic Evaluations Database identified 11 relevant economic evaluations. Nine of these 11 economic evaluations were either cost-effectiveness analyses or cost-utility analyses conducted within the framework of a decision model (Beard 2006, Edwards 2008, Edwards 2005, Furiak 2009, Geitona 2008, Kongsakon 2005, McIntyre 2010, Mortimer 2003, Obradovic 2007).

One economic evaluation was a cost analysis conducted within the framework of a retrospective cohort study utilising Medicaid medical and pharmacy claims data and focusing on children and adolescents treated with antipsychotic agents (including five atypical antipsychotics covered in this review), amongst whom 8.7% of the treated cohort were diagnosed with schizophrenia and 27% with 'other psychotic disorders'

(Jerrell 2009). The other economic evaluation we identified could not be classified (Mould 2009 – Spanish language article, not translated).

Only one economic evaluation involved a head-to-head comparison considered in this review (Comparison 4). This was a cost-utility analysis (Markov model) comparing the long-term impact of risperidone versus olanzapine in the treatment of patients with an established history of schizophrenia (Beard 2006). This analysis adopted a German health care system perspective and estimated direct health care costs and quality adjusted life years (QALYs), utilising data collected from a single study to inform each individual model parameter (relevant studies were assembled using a literature review). Costs and QALYs were not combined because olanzapine was found to dominate risperidone (i.e. olanzapine was associated with more QALYs and lower costs compared with risperidone). The effectiveness result (QALYs) from this economic evaluation is consistent with evidence from our review of RCTs, which suggested (with caveats) a better quality of life of participants treated with olanzapine compared with risperidone.

Eight other economic evaluations included risperidone in comparing several atypical antipsychotics (Edwards 2008, Edwards 2005, Furiak 2009, Geitona 2008, Kongsakon 2005, McIntyre 2010, Mortimer 2003, Obradovic 2007). Variations in selection of comparators, methods, assumptions and data sources across these 8 economic evaluations makes it difficult to draw reliable inferences based on their results (without having subjected these analyses to a formal systematic review process). Bearing in mind this caveat, with one exception (Edwards 2005) the results of the multiple treatment comparisons considered across these 8 economic evaluations consistently favoured other atypical antipsychotics over risperidone, from an economic perspective.

It is important to highlight that we did not subject any of the 11 identified economic evaluations to critical appraisal and we do not attempt to draw any firm or general conclusions regarding the relative costs or efficiency of the atypical antipsychotics compared. However, it is clear that the available economic evidence for risperidone, compared with other atypical antipsychotics in the treatment of patients with schizophrenia is, at best, equivocal. End users of this review will need to assess the extent to which methods and results of identified economic evaluations may be applicable (or transferable) to their own setting.

3.4.3. Researcher time input to developing economic commentaries
On average (median), development of an economic commentary was completed (time on task) in 64 minutes (N=5; Median = 64.0; Mean = 91.8, s.d. = 57.3; Range = 41.0 to 167.0).

3.5. Aggregate researcher time input to development of economic commentaries

On average (median), the aggregate researcher time input (time on task) required to complete all processes undertaken in this study (selected reviews only) – comprising: development and application of two sets of NHS EED and HEED search strategies; processing of both sets of search results (where the latter comprises: initial screening of NHS EED and HEED records; assessment of eligibility based on NHS EED and HEED records and, if required, abstracts and/or full-text articles; and classification of eligible economic evaluations and economic analyses); and development of the economic commentary –was 210 minutes per review (N=5; Median = 210; Mean = 245.6, s.d. = 140.3; Range = 93.0 to 450.0).

3.6. Yields of eligible records from original searches of Medline, Embase and Central

Appendix 6 (Tables A6.1 and A6.2) provides full details of the yields of records of economic evaluations assessed as eligible from original searches of Medline (with and without RCT search filter), Embase (with and without RCT search filter) and Central. The results of this analysis provide some empirical evidence to support the claim that incorporation of RCT search filters into search strategies applied in general biomedical databases with the aim of locating both eligible randomised controlled trials and eligible economic evaluations are likely to locate records of eligible economic evaluations conducted within the framework of a randomised controlled trial, but not records of economic evaluations conducted within the framework of other empirical study designs or those conducted within the framework of a decision model (see Shemilt 2008). The results also confirm that search strategies applied in general biomedical databases with the aim of locating eligible studies of effects are unlikely to locate records of eligible economic analyses (economic burden/cost-of-illness) because they combine search terms designed to capture 'Population(s)' concepts with search terms designed to capture 'Intervention(s)' concepts (and possibly also search terms designed to capture 'Comparison(s)' concepts.

Together, these results support the case for conducting supplementary searches of NHS EED and HEED in Cochrane reviews that include an aim to incorporate economic perspectives and evidence (whether this takes the form of economic commentary or an integrated systematic review of economic evidence). They also provide evidence in

support of the process recommended in this report for conducting searches of NHS EED and HEED to inform development of economic commentary for Cochrane intervention reviews (see 'Executive Summary', Section E4) and detailed recommendations for designing such searches (see 'Executive Summary', Section E5 and/or 'Discussion and recommendations' below, esp. Recommendations 1 and 2).

3.7. Critical appraisal of eligible economic evaluations and implications for economic commentaries

[# To be completed – see 'Methods' Section 2.7 and Appendix 7]

Discussion and recommendations

This study aimed to develop and evaluate methods processes that can be used to incorporate electronic searches of NHS EED and HEED into Cochrane intervention reviews and to use the results of these searches to inform development of economic commentaries to be integrated into 'Background' and 'Discussion' sections of such reviews. This section discusses principal findings of the study and offers provisional recommendations for consideration by the Cochrane Editorial Unit and Co-coordinating Editors of Cochrane Review Groups.

It has been proposed that economic commentaries could comprise two main elements:

1. Information regarding the economic burden/ cost-of-illness of the health condition addressed by the experimental intervention(s) being studied, based on economic analyses that include such information (to be included in the 'Background' sub-section on 'Description of the condition'); and

2. Information regarding the *prima facie* case that an intervention might be judged favourably (or unfavourably) from an economic point of view, based on the findings of relevant full and partial economic evaluations (to be included in the 'Discussion' section).

This study indicates that this proposal is feasible.

It is clear based on the experience of conducting this study that NHS EED and HEED search strategies will need to be constructed differently depending upon which of the above two types of information/ types of analyses (1 and 2) are being sought.

- Recommendation 1: NHS EED and HEED search strategies aiming to locate economic analyses that report information regarding the economic burden/ cost-of-illness of the health condition being addressed should use keyword search terms designed to capture 'Population' concepts. These search strategies can be adapted from 'Population' keyword search terms that form part of those search strategies used to identify relevant studies of effects.

- Recommendation 2: NHS EED and HEED search strategies aiming to locate relevant full and partial economic evaluations (i.e. those that both compare the experimental intervention(s) and eligible comparator(s) studied in the intervention review and that meet eligibility criteria set with respect to population(s)) should use at least keyword search terms designed to capture 'Intervention' concepts. These search strategies can be adapted from 'Intervention' keyword search terms that form part of search strategies used to identify relevant studies of effects.

With respect to 'Recommendation 2', search strategies developed for this purpose would ideally combine keyword search terms designed to capture 'Intervention' concepts with keyword search terms designed to capture 'Comparison' concepts and 'Population' concepts, using the 'AND' operator. However, this will often be precluded by limitations of the current NHS EED and HEED search interfaces.

As well as requiring different search strategies, NHS EED and HEED searches may legitimately differ in terms of their scope, depending on which of the above two types of information/ types of analyses (1 or 2) are being sought. Searches of that aim to locate economic analyses (economic burden/cost-of-illness) often generate relatively large record sets[24], which has resource implications in terms of the time needed to process these search results. The approach adopted for this study was to make searches as sensitive as possible (within available resources) in order to identify all relevant and potentially useful economic analyses (economic burden/ cost-of-illness) meeting eligibility criteria. This approach was adopted due to the need to address specific research questions relating to the degree of overlap between NHS EED and HEED in their coverage of relevant and potentially useful literature. However, for Cochrane intervention reviews, a pragmatic strategy (given the intended brevity of economic commentary regarding the economic burden/cost-of-illness of the health condition addressed) would be to seek to identify the few economic analyses that appear most useful to inform development of the economic commentary.

We suggest that, given the international audience of end users of Cochrane reviews, comprising different constituencies of health care decision makers (e.g. policy-makers, clinicians/professionals and consumers), key characteristics of economic analyses well-suited to inform economic commentary regarding 'economic burden of health condition/cost-of-illness' are: most recent analyses available; focus on international comparisons (e.g. estimates applicable to a range of countries or global regions); and inclusion of estimates made from a societal perspective in addition to those made from a health care perspective (i.e. focus on economic burden/ cost-of-illness' to society as a whole, including estimates of the indirect burden/costs accruing to a range of economic sectors and/or to patients/ their families, alongside direct burden/costs accruing to the health system, or to providers/payers within the health system). If international comparative analyses are not available, the next-best alternative would be to identify a few recent analyses that report national-level estimates for single countries located in different global regions (again, preferably also including estimates made from a societal perspective).

With respect to search strategies applied in NHS EED, it is currently reasonable to append terms that restrict searches for economic analyses (economic burden/ cost-of-illness) to citation only records of 'Cost studies' and 'Reviews of economic evaluations'

[24] In comparison to searches for relevant economic evaluations.

(i.e. <cost:ty OR review:ty>). Similarly, with respect to search strategies applied in HEED, it is reasonable to append terms that restrict searches to (field-coded abstract or citation only) records of cost-of-illness studies and/or reviews of applied studies (i.e. <Type Of Econ Eval: 'COST OF ILLNESS'> OR <Type Of Article: 'REVIEW OF APPLIED STUDIES'> in a compound search). For both NHS EED and HEED, appending terms that restrict searches in this way may only be judged necessary if record sets retrieved by search strategies comprising only keyword search terms designed to capture 'Population' concepts are judged too large to manage within the scope of time available to be allocated to screening records for this purpose. With respect to the screening process, the implication of the approach described above is that authors should be highly selective about which NHS EED and HEED records/articles will be selected for use to inform development of the economic commentary (economic burden/ cost-of-illness).

In comparison, searches of NHS EED and HEED that aim to locate relevant economic evaluations are unlikely, in most cases, to generate large records sets. In general, this makes the process of screening retrieved records sets manageable. For searches conducted for this purpose, it is important to identify *all* relevant economic evaluations in order to minimise bias that may be introduced into economic commentaries as result of failing to draw on relevant records/articles. The strategy adopted in the current study was to identify all available full and partial economic evaluations, regardless of the framework used and sources of data utilised. It is arguably reasonable to extend this strategy to searches conducted for the purpose of identifying relevant economic evaluations to inform economic commentaries in Cochrane intervention reviews.

This study also indicates that, for many Cochrane intervention reviews, few or no relevant economic evaluations will have been published. In this case, the process of conducting searches for such evaluations serves primarily to confirm that no relevant published economic evaluations are available. Depending on *ex ante* expectations regarding the direction and magnitude of cost differences between the alternatives being compared in a review, identifying a lack of relevant economic evaluations may indicate a gap in the overall evidence base that needs to be addressed (see also Recommendation 24, below).

- Recommendation 3: Searches of NHS EED and HEED aiming to locate economic analyses that report information regarding the economic burden/ cost-of-illness of the health condition being addressed should aim to identify the few analyses judged most useful to inform economic commentary on this issue. In general, economic analyses likely to be most useful are recently conducted applied cost-of-illness studies or reviews of applied cost-of-illness studies that focus on international comparisons and that include estimates of societal burden/cost alongside burden/cost to health care systems.

- Recommendation 4: Searches of NHS EED and HEED aiming to locate relevant economic evaluations should be sufficiently sensitive to locate *all* available, relevant published economic evaluations.

Results of this study that relate to comparative yields of NHS EED and HEED records (unique yields and duplicate records) indicate the current value of searching both databases for the purposes described above. However, is important to highlight that the Centre for Reviews and Dissemination, which manages NHS EED, is in the process of implementing changes to this database that will result in all records except for structured abstract records (and provisional abstract records) of full economic evaluations being permanently deleted. Once implemented, this will make the case for searching both databases even more compelling with respect to the aim of identifying *all* relevant economic evaluations to inform development of economic commentaries, since NHS EED will no longer include records of relevant cost analyses. However, with respect to the aim of identifying economic analyses that report information regarding the economic burden/ cost-of-illness of the health condition being addressed, the change will mean that searches of NHS EED will no longer generate useful record sets.

- Recommendation 5: Authors should conduct searches of both NHS EED and HEED for the purpose of identifying *all* relevant published economic evaluations.

- Recommendation 6: At present, authors should conduct searches of both NHS EED and HEED for the purpose of identifying the most useful economic analyses containing information regarding the economic burden/ cost-of-illness of the health condition being addressed.

- Recommendation 7: Once NHS EED no longer includes records other than structured abstract records (and provisional abstract records) of full economic evaluations (i.e. from [#Insert date]), authors should conduct searches of HEED only for the purpose of identifying the most useful economic analyses containing information regarding the economic burden/ cost-of-illness of the health condition being addressed.

Assessing the eligibility of relevant economic evaluations and classifying them by analysis type and framework used can be a time consuming process that requires both care and a basic knowledge of different types of economic evaluation (analysis type and framework) and the populations, interventions and comparisons being considered in the Cochrane intervention review. First, the difficulty of completing these tasks is likely to depend on the availability and level of detail of information needed to inform assessments of eligibility and classifications in NHS EED/HEED records and also on the number and complexity of relevant eligibility criteria set in the corresponding intervention review. Second, there are inconsistencies across articles in descriptions of the analysis type used in an economic evaluation, reflecting different conventions used in different countries. For example, it is relatively common in the United States for

authors to describe a study as a cost-benefit analysis when the study does not value both costs and effects in commensurate (usually monetary) units (i.e. a study that would usually be classified as cost-effectiveness analyses in most other countries). Third, it is likely to be necessary in a significant minority of cases (around 25% in this study), to examine the corresponding article abstract and/or full-text in order to complete the processes of eligibility assessment (relevance) and classification of economic evaluations (analysis type) with confidence; NHS EED and HEED records are often (but not always) sufficient.

Use of an established classification scheme (Drummond 2005) combined with close reference to descriptions of the main types of full and partial economic evaluation published in Chapter 15 of the Cochrane Interventions Handbook (Shemilt 2008) may prove useful in helping authors less familiar with economic evaluations to classify economic evaluations in a way that is consistent across intervention reviews. Independent duplicate screening and classification by two researchers, with resolution of disagreements through subsequent discussion, is also likely to help in this respect, and is consistent with recommended best practice for systematic reviews (Higgins 2008, Shea 2007). It may sometimes be necessary to consult with a health economist advisor to resolve any persisting uncertainties regarding classification by analysis type (assuming there is no health economist within the author team). The proposed development of a network of CRG (and Centre)-based health economists should, in theory, increase direct access for Cochrane authors to specialist economics methods advice via their CRG.

With respect to screening of economic analyses that report information regarding the economic burden/ cost-of-illness of the health condition being addressed, intensive screening (and classification) is unlikely to be warranted beyond establishing, through examination of NHS EED and/or HEED records and/or the corresponding article abstract/full text, that the economic analysis does indeed relate to the health condition of interest and is a good candidate (see Recommendation 3) to inform development of related economic commentary.

- Recommendation 8: Where available, authors should retrieve and refer to abstracts and/or full-texts of corresponding articles to complete assessments of eligibility (and classification, in the case of economic evaluations), if the NHS EED and/or HEED record proves insufficient for this purpose.

- Recommendation 9: Screening NHS EED and HEED records and corresponding article abstracts and/or full-texts (if required) to assess the eligibility of economic evaluations and to classify the type of analysis undertaken should be completed independently by two researchers, with resolution of any disagreements through discussion.

- Recommendation 10: Assessment of the eligibility of economic evaluations should be based on those eligibility criteria set for the corresponding intervention review that relate to Population(s), Interventions(s) and Comparison(s).

- Recommendation 11: In addition to a clear understanding of relevant eligibility criteria set for the corresponding intervention review to inform assessments of eligibility of economic evaluations, classification of eligible economic evaluations can be assisted by an established classification scheme for types of economic evaluation (analysis type) and descriptions of the main types of full economic evaluation published in Chapter 15 of the *Cochrane Handbook for Systematic Reviews of Interventions*.

- Recommendation 12: Screening the results of searches aiming to locate economic analyses (economic burden/ cost-of-illness) should focus primarily on confirming the relevance of each record/analysis to the health condition of interest and also that it is a good candidate (see Recommendation 3) to inform development of related economic commentary. It is not judged necessary that screening of the results of these searches should be completed independently by two researchers.

It may be argued that the time taken (time on task) in this study to complete the processes of screening records/articles and classifying economic evaluations by analysis type are unrepresentative of time that authors of Cochrane reviews would take to complete these processes, since the researcher undertaking this study (IS) has a level of expertise/experience in health economics. This is likely to be true to an extent (clearly, authors with more advanced health economics expertise, or at least a basic familiarity with related principles, concepts and methods, are likely to require less time to complete these processes than those without). However, on the other hand the researcher undertaking this study (IS) has no clinical expertise/ experience in any of the health care topic areas covered by included Cochrane intervention reviews, whilst Cochrane author teams usually do include such expertise/ experience. Having relevant clinical expertise/experience is likely to speed up the process of assessing the eligibility of records/analyses of both economic evaluations (with reference to eligibility criteria set in the corresponding review) and economic analyses (with reference to an understanding of the health condition being addressed), and may offset any limited expertise/experience in health economics (that would, arguably, slow down the process of classification of economic evaluations by analysis type and framework used). The latter considerations do not negate the need for authors of Cochrane reviews intending to implement the methods process recommended in this report to participate in training to be developed by the Campbell and Cochrane Economics Methods Group to support implementation of the process.

If available, NHS EED structured abstract records and HEED field-coded abstract records of economic evaluations proved very useful to inform the process of developing economic commentary focused on summarising the *prima facie* case that an intervention might be judged favourably (or unfavourably) from an economic point of view, based on the principal findings of relevant full and partial economic evaluations (to be included in the 'Discussion' section). However, these records were not always judged sufficient, since information that could usefully supplement that obtained from NHS EED structured abstract records and/or HEED 'field-coded abstract records' was frequently identified in full-texts of corresponding articles. Use of supplementary information collected from corresponding full-text articles of eligible economic evaluations was found to be particularly useful to inform economic commentaries if only a corresponding HEED field-coded abstract record was available, since the full-text could clarify details of (for example) sample/patient characteristics or included cost components, where these were not described in detail in the HEED field-coded abstract record. Our opinion, based on the experience of conducting this study, is that information available in NHS EED structured abstract records is often more detailed than in HEED field-coded abstract records, and also that the standardised format of NHS EED structured abstract records makes it easier to locate and extract information likely to be judged relevant and useful to include in an economic commentary.

Where both NHS EED structured abstract records and HEED field-coded abstract records of economic evaluations were available for a given article (i.e. duplicate records), it proved useful to draw on both records to inform the economic commentary. This was found useful with respect to both confirming that key information was consistent between records and identifying key information reported in one record but not in the other. For example, for the economic commentary developed for the review by Kamal 2011, the NHS EED structured abstract record of the economic evaluation by Inoue 2006 included a range of key information that was not covered in the corresponding HEED field-coded abstract record, including: doses of cilostazol and aspirin; characteristics of the patient population (hypothetical cohort) modelled; components of direct health care costs included in the analysis; sources of data used to populate clinical effectiveness, safety and other model parameters; and additional details of results and sensitivity analyses. Similarly, for the economic commentary developed for the review by Dasari 2011, the NHS EED structured abstract record of the economic evaluation by Young-Fadok 2001 included key details of: the empirical study alongside which the economic evaluation was conducted; the analytic perspective adopted and the fact that indirect costs were included in the analysis in addition to direct health care costs - none of these details were available in the corresponding HEED field-coded abstract record. In this study, we found no examples of HEED field-coded abstract records including key information that was not also contained in the corresponding NHS EED structured abstract record. Again, we judge that the latter

finding reflects the finer level of detail currently available in NHS EED structured abstract records, compared with HEED field-coded abstract records.

We identified only one instance of serious discrepancy between an NHS EED structured abstract record and a corresponding HEED field-coded abstract record in this study. This was found in the respective records of the Inoue 2006 economic evaluation, identified as relevant to the Kamal 2011 review. The HEED field-coded abstract record stated that: "The aspirin strategy was the dominant strategy when compared to the untreated [no prophylaxis] group and the cilostazol group." However, the NHS EED structured abstract record stated that: "No prophylaxis was found to be dominated by the aspirin strategy (i.e. the aspirin strategy was both cheaper and more effective than no prophylaxis). Compared with aspirin, the additional cost per QALY gained was JPY 1,792,216 using the cilostazol strategy." This discrepancy could only be resolved beyond doubt by referring to the corresponding full-text article, which confirmed that the NHS EED structured abstract record was accurate, whilst the HEED field-coded abstract record was inaccurate[25].

NHS EED records of economic analyses (economic burden/cost-of-illness) are not at all useful to inform economic commentary on this issue (for inclusion in the 'Background' section), since these records are invariably citation only records. HEED records of such economic analyses are frequently field-coded abstract records, which contain a comparable amount and level of detail as HEED field-coded abstract records of economic evaluations, and which are therefore comparably useful to inform economic commentary on economic burden/cost-of-illness. However, information that could usefully supplement that obtained from HEED field-coded abstract records was identified frequently in corresponding full-text articles (as was the case with respect to economic evaluations).

- Recommendation 13: Where available, authors should draw on the contents of (both) NHS EED structured abstract records and/or HEED field-coded abstract records to inform the development of economic commentaries.

- Recommendation 14: Where available, authors should additionally draw on corresponding full-text articles to inform the development of economic commentaries. Use of corresponding full-text articles alongside NHS EED structured abstract records and/or HEED field-coded abstract records serves two purposes: identifying useful supplementary information that is not included in the NHS EED or HEED record and resolving any discrepancies between NHS EED or HEED records (if both are available). If NHS EED and/or HEED records

[25] The HEED field-coded abstract record was also internally inconsistent, since the sentence that immediately followed the one quoted in the main text stated that "When compared to the aspirin group, the incremental cost-effectiveness ratio was Yen1.79 million for the cilostazol group".

are (both) citation only records, corresponding abstracts and/or full-text articles will be the primary source for development of economic commentaries.

A hypothesis explored in this study was that economic commentaries can be developed without subjecting source economic analyses and/or economic evaluations to formal critical appraisal (i.e. assessments of study limitations/ methodological quality). Our overall conclusion is that it is feasible to develop economic commentaries without subjecting source economic analyses and/or economic evaluations to formal critical appraisal, but that if this is the case, an economic commentary should *always* be accompanied by appropriate caveats, given the potential for unreliable/ biased economic analyses and/or economic evaluations to inform commentaries that contain unreliable messages. With respect to the former (i.e. development of economic commentary regarding the economic burden/ cost-of-illness of the health condition addressed by the experimental intervention(s) being studied), it seems reasonable that source economic analyses do *not* need to be subjected to formal critical appraisal, as this is consistent with the approach adopted to all other sources cited in the 'Background' section of intervention reviews. However, this does not preclude authors from examining descriptions of methods used to conduct such analyses (in HEED records and/or corresponding article abstracts/ full texts) in order to satisfy themselves that the methods used, and thus findings used to inform the economic commentary, are at least credible[26].

With respect to the latter (i.e. development of economic commentary regarding the focused on summarising the *prima facie* case that an intervention might be judged favourably (or unfavourably) from an economic point of view) the case for or against subjecting source full and partial economic evaluations to formal critical appraisal seems less clear cut. One option is *not* to undertake formal critical appraisal of source economic evaluations, but to include clear statements to make it clear to end users of reviews that formal critical appraisal has not been undertaken. The other option is to undertake formal critical appraisal of source economic evaluations, informed by application of a recognised 'quality assessment' checklist, and to expand the scope of the economic commentary to incorporate a brief summary of the main strengths and/or limitations identified across economic evaluations (or for each). Critical appraisal of economic evaluations is a time consuming process when done rigorously, even when informed by application of a relatively brief checklist that is accompanied by a clear coding guide (as in this study) and undertaken by researchers with expertise/experience in health economic evaluation. The time needed to complete the critical appraisal process would also (at least) double, if undertaken independently by two researchers and with any disagreements in coding checklists resolved through discussion. [#Integrate further discussion here once critical appraisal of eligible economic evaluations has been completed??]. The choice between these two options

[26] Presumably, authors examine all other sources cited in the 'Background' section to evaluate their credibility.

may, in practice, depend on the numbers of eligible economic evaluations that would need to be appraised, the time available to be allocated to the overall process of developing economic commentaries, and the availability of health economics expertise within the author team (which is probably needed to complete the critical appraisal process). Whichever option is chosen, it is important to ensure that all 'evidence statements' regarding the *prima facie* case that an intervention might be judged favourably (or unfavourably) from an economic point of view should be presented as 'tentative' and accompanied by appropriate caveats. Suggested forms of words that may be used for this purpose are included in the economic commentaries presented in this report (see 'Results', Section 3.4.2).

- Recommendation 15: In line with other sources cited in the 'Background' section of a review, it is not necessary to subject those economic analyses selected as sources to inform development of economic commentary regarding economic burden/ cost-of-illness of the health condition to formal critical appraisal.

- Recommendation 16: Authors of reviews will need to decide whether to subject economic evaluations used as sources to inform development of economic commentary regarding the *prima facie* case that an intervention might be judged favourably (or unfavourably) from an economic point of view to formal critical appraisal. This decision is likely to depend on the number of economic evaluations to be appraised, the time available to be allocated to the overall process of developing economic commentaries, and the availability of health economics expertise within the author team.

- Recommendation 17: If authors of reviews decide not to subject source economic evaluations to formal critical appraisal should include an explicit statement of this fact in the related economic commentary.

- Recommendation 18: If authors decide to subject source economic evaluations to formal critical appraisal, a recognised checklist should be used to inform this process. The 'study limitations' component of the methodology checklist that is recommended for critical appraisal of economic evaluations by the National Institute for Health and Clinical Excellence may be used for this purpose (NICE 2009). Checklist(s) should be completed independently by two researchers, with resolution of any disagreements through discussion.

- Recommendation 19: If authors decide to subject source economic evaluations to formal critical appraisal, they should include a brief summary of the main strengths and limitations of these evaluations in the economic commentary. The consensus judgements made by researchers in using the checklist (recorded in the comments section of the checklist) can be used to inform development of this summary.

Clearly, the precise form of economic commentaries for Cochrane intervention reviews will need to be determined for each individual review. However, the experience of conducting this study has identified key elements that may be recommended for inclusion in economic commentaries.

- Recommendation 20: Economic commentary regarding economic burden/ cost-of-illness of the health condition *may* usefully include the following information: a brief, general statement of the scale of economic burden/ cost-of-illness to health care systems, patients and/or their families and/or society as a whole; monetised estimate(s) of the scale of economic burden to health care systems; monetised estimate(s) of the scale of economic burden to patients and/or their families; monetised estimate(s) of the scale of economic burden to societies as a whole. Economic commentary regarding economic burden/ cost-of-illness of the health condition *should* include: details of currency and price year for any monetised estimates.

- Recommendation21: Economic commentary focusing on the *prima facie* case that an intervention might be judged favourably (or unfavourably) from an economic point of view *should* include brief details of the: electronic health economics literature databases searched; number of relevant economic evaluations identified; primary types of analysis used in relevant economic evaluations (i.e. cost analysis; cost-effectiveness analysis; cost-utility analysis; cost-benefit analysis); frameworks used to assemble data for relevant economic evaluations (i.e. conducted within the framework of a randomised controlled trial; conducted using the framework of a decision model); analytic perspective and time horizon adopted for costs and (if applicable) effects; main cost categories included in the analysis (e.g. hospital care costs, direct health care costs; indirect non-health care costs); currency and price year; principal conclusions made by authors of included economic evaluations (base case analysis); uncertainty regarding authors' principal conclusions based on any sensitivity analyses conducted. Such commentary should also include a brief description of any tentative inferences that can be drawn regarding the *prima facie* case that an intervention might be judged favourably (or unfavourably) from an economic point of view *and* appropriate caveats for any tentative inferences. If only one or two relevant economic evaluations are identified, commentary focusing on this issue *may* include principal results collected from each study that estimate the relative costs and/or relative efficiency of the alternatives compared (e.g. measures of incremental cost, incremental cost per unit of effect, or incremental cost per QALY intervention(s) versus comparator(s)). In this case, the commentary should also include details of the currency and price year applicable to all monetised estimates. Where several economic relevant economic evaluations are identified, it may not be judged

feasible to summarise principal results collected from each study; instead it is recommended to focus solely on summarising authors' principal conclusions.

- Recommendation22: Where economic commentary includes monetised estimates of economic burden/cost-of-illness, costs and/or relative efficiency collected from one or more published studies conducted in different countries and/or at different times, authors may consider presenting estimates that are adjusted to a common target currency and price year, in order to facilitate comparison of estimates between studies. A free, web-based cost conversion tool that may be used for this purpose is available online at http://eppi.ioe.ac.uk/costconversion/default.aspx. This web-page includes a link to an article that includes guidance on use of the tool for this specific purpose (Shemilt 2010).

- Recommendation23: All source published reports of economic analyses and/or economic evaluations used to inform development of economic commentary should, at minimum, be cited in 'Additional references'. With respect to published reports of source economic evaluations, authors may wish to consider providing a separate, annotated bibliography as an appendix to the review. If this option is chosen, annotation that could usefully supplement each citation would describe key characteristics of source economic evaluations. At minimum, the annotation should comprise the primary type of analysis and type of framework used (see Recommendation 21). In addition, it could usefully include the main cost categories included in the analysis (see Recommendation 21); and the analytic perspectives and time horizons adopted for costs and (if applicable) effects.

Alongside this study we have sought to develop criteria that may be used to prioritise Cochrane intervention reviews in which it is likely to add most value to develop an economic commentary, based on records/articles identified by undertaking supplementary searches of NHS EED and HEED. Our provisional recommendation is that it is likely to add most value to incorporate supplementary searches of NHS EED and HEED in order to develop economic commentaries where:

- The comparator(s) being considered include alternative management strategies that are used in current practice, i.e. the comparator(s) are not limited to placebo only;

- Important cost differences are expected between the experimental intervention(s) and comparator(s) being considered.

The rationale for assigning a low priority to reviews that focus solely on (one or more) pairwise comparison(s) between experimental intervention(s) and placebo is that evidence for differences between an experimental intervention and placebo in terms of

resource use, costs and/or efficiency are likely to be highly limited in terms of their usefulness to inform 'real world' adoption or resource allocation decisions. The rationale for assigning a low priority to reviews that compare experimental intervention(s) and comparator(s) that are not expected to differ importantly in terms of resource use, costs and/or efficiency is that, in these circumstances, economic evidence is unlikely to form an important component of the basis for decision-making.

Ex ante judgements regarding the likelihood that there will be important cost differences between the experimental intervention(s) and comparator(s) being considered may sometimes be difficult to make. However, in general such judgements can be informed by thinking about (i) the types and amounts of resources that are likely to be needed to produce the experimental intervention(s), compared with those needed to produce alternative management strategies used in current practice (i.e. resource inputs, or upfront costs); and (ii) the potential impact of the experimental intervention(s), compared with alternative management strategies, on health outcomes (and possibly other relevant non-health outcomes). With respect to the latter, the focus is on thinking about the extent to which potential differences in health (and other) outcomes are likely to lead to associated differences in resource use and costs (i.e. resource consequences, or downstream costs). For example, if it is hypothesised, or expected, that use of a new surgical technique is likely to result in fewer complications and/or secondary procedures, compared with a current standard technique, and the resources needed to manage complications and/or secondary procedures are considerable and/or costly, this implies there is likely to be an important difference between the new surgical technique and the current standard technique in terms of resource use and/or costs. Similarly, if it is hypothesised that a new drug for use in the treatment of patients with epilepsy is likely to result in fewer and/or lower severity epileptic seizures, compared with current alternative drugs, and the resources needed to manage severe seizures are considerable and/or costly, then this implies there is likely to be an important difference between the new drug and current alternative drugs in terms of resource use and/or costs.

In considering the likelihood of important differences between the experimental intervention(s) and comparator(s) in terms of both resource inputs/upfront costs and resource consequences/downstream costs, one factor to consider is the expected size of resource use and/or cost differences per patient. However, considerations of the importance of potential cost differences may also relate to the prevalence of the health condition. This is because relatively small expected differences in the size of resource use and/or cost differences per patient may be expected to translate into large (and therefore important) differences in overall resource utilisation and/or associated costs when applied to large numbers of patients.

Collectively, the expected size of resource use and/or cost differences per patient and expected size of differences in overall resource utilisation and/or associated costs can

be conceptualised as issues of magnitude. However, alongside issues of magnitude, it is also necessary to consider issues of analytic perspective and time horizon. With respect to analytic perspective, it is important to think about which categories of resource use and costs are likely to be considered important to different types of end users. For Cochrane intervention reviews, which aim to inform decisions made by policy-makers, clinicians and consumers, it is likely to be important to consider both health care costs and wider societal costs, including those accruing to patients and their families (and possibly also to other economic sectors), alongside issues of the magnitude of expected cost differences. With respect to time horizon, it is important to consider the length of time over which expected cost differences that may reasonably be attributed to the choice between experimental intervention(s) and comparator(s) are expected to occur, alongside issues of magnitude and analytic perspective. For long-term, chronic health conditions, the differential effects of interventions may be expected to result in resource use and cost differences accruing over a long period; possibly over the patient's lifetime.

In considering the extent to which important resource use and cost differences are expected between the experimental intervention(s) and comparator(s) being considered in a review, it can be helpful to develop a clinical event pathway description to provide a conceptual diagram of the main pathways of clinical events that have distinct resource implications or health outcomes associated with them, from the point of introduction of the interventions being compared, through subsequent changes in the management of patients, to final health outcomes. Further information on the use of clinical event pathways to help authors conceptualise economic components of reviews is available in Chapter 15 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Shemilt 2008).

A further, purely pragmatic proposal is that it may be more feasible for Cochrane author teams to develop an economic commentary for their intervention reviews, based on records/articles identified by undertaking supplementary searches of NHS EED and HEED, when updating a published review rather than preparing a new review that has not previously been published in the *Cochrane Database of Systematic Reviews* (Shemilt 2008). Finally, where Cochrane reviews do incorporate economic commentary of the form proposed in the recommendations above, Cochrane Review Groups (CRGs) may judge it advisable to seek peer review for the commentary from either the designated economic advisor to the CRG (if available), the designated CRG-based member of the network of CRG and Centre-based individuals for economics methods (once implemented), or members of the Campbell and Cochrane Economics Methods Group (CCEMG). The CCEMG will (on request) aim to either provide such peer review directly (within available resources) or to identify a suitable peer reviewer from amongst its active membership (i.e. health economist members who have previously indicated a willingness to provide peer review to support the production of economics components of Cochrane intervention reviews in specified topic areas).

- Recommendation24: Cochrane intervention reviews that should be prioritised for encouraging author teams to develop an economic commentary are those that include comparison(s) of experimental intervention(s) with one or more alternative management strategies (i.e. not focused exclusively on comparison(s) between experimental intervention(s) and placebo) and in which important cost differences can be expected between experimental intervention(s) and comparator(s), for at least one of three reasons: large difference in upfront costs of interventions; large difference in downstream costs of managing subsequent events (short or long-term); small cost difference (upfront costs and/or downstream costs) but large patient populations affected. . Additionally, update reviews may be prioritised for development of economic commentaries over new reviews.
- Recommendation 25: CRGs should consider seeking specialist peer review for economic commentaries of the form proposed in this study. If a CRG does not have access to specialist review from CRG-linked health economists, they should contact the Campbell and Cochrane Economics Methods Group for this purpose.

References

Craig 2007
Craig D, Rice S. *CRD Report 6: NHS Economic Evaluation Database Handbook* (3rd edition). York: Centre for Reviews and Dissemination, University of York, 2007.

Drummond 2005
Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes* (3rd edition), pp.11. Oxford: Oxford University Press, 2005.

Higgins 2008
Higgins JPT, Deeks JJ (editors). Chapter 7: Selecting studies and collecting data. In: JPT. Higgins and S. Green (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: John Wiley & Sons, 2008.

NICE 2009
National Institute of Health and Clinical Excellence (NICE). Appendix H: Methodology checklist: economic evaluations - Section 2: Study limitations. In: NICE. *The Guidelines Manual: Appendices*, pp. 194-207. London: NICE, 2009.

Shea 2007
Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, Porter AC, Tugwell P, Moher D, Bouter LM. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Medical Research Methodology* 2007; 7:10.

Shemilt 2008
Shemilt I, Mugford M, Byford S, Drummond M, Eisenstein E, Knapp M, Mallender J, McDaid D, Vale L, Walker D. Chapter 15: Incorporating economics evidence. In: JPT. Higgins and S. Green (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester: John Wiley & Sons, 2008.

Shemilt 2010
Shemilt I, Thomas J, Morciano M. A web-based tool for adjusting costs to a specific target currency and price year. *Evidence and Policy* 2010; 6(1): 51-59.

Appendix 1. Included intervention reviews

Cochrane Database of Systematic Reviews, Issue 1, 2011

Citation	*CRG*	*Included*
Paley CA, Johnson MI, Tashani OA, Bagnall AM. Acupuncture for cancer pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007753. DOI: 10.1002/14651858.CD007753.pub2.	Pain, Palliative and Supportive Care Group	✓
Smith CA, Zhu X, He L, Song J. Acupuncture for primary dysmenorrhoea. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007854. DOI: 10.1002/14651858.CD007854.pub2.	Menstrual Disorders and Subfertility Group	✓
Galaal K, Godfrey K, Naik R, Kucukmetin A, Bryant A. Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD006812. DOI: 10.1002/14651858.CD006812.pub2.	Gynaecological Cancer Group	✓
Kuhle S, Urschitz MS. Anti-inflammatorymedications for obstructive sleep apnea in children. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007074. DOI: 10.1002/14651858.CD007074.pub2.	Airways Group	✓
Showell MG, Brown J, Yazdani A, Stankiewicz MT, Hart RJ. Antioxidants for male subfertility. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007411. DOI: 10.1002/14651858.CD007411.pub2.	Menstrual Disorders and Subfertility Group	✓
Liu J, Wang L. Baclofen for alcohol withdrawal. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art.No.: CD008502. DOI: 10.1002/14651858.CD008502.pub2.	Drugs and Alcohol Group	✓
Waseem Z, Boulias C, Gordon A, Ismail F, Sheean G, Furlan AD. Botulinum toxin injections for low-back pain and sciatica. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008257. DOI: 10.1002/14651858.CD008257.pub2.	Back Group	✓
Kamal AK, Naqvi I, Husain MR, Khealani BA. Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008076. DOI: 10.1002/14651858.CD008076.pub2.	Stroke Group	✓
Aboumarzouk OM, Agarwal T, Antakia R, Shariff U, Nelson RL. Cisapride for Intestinal Constipation. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007780. DOI: 10.1002/14651858.CD007780.pub2.	Colorectal Cancer Group	✓
Martin M, Clare L, Altgassen AM, Cameron MH, Zehnder F. Cognition-based interventions for healthy older people and people with mild cognitive impairment. *Cochrane Database of Systematic Reviews* 2011, Issue 1.	Dementia and Cognitive Improvement Group	✓

Art. No.: CD006220. DOI: 10.1002/14651858.CD006220.pub2.		
Morag I, Ohlsson A. Cycled light in the intensive care unit for preterm and low birth weight infants. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD006982. DOI: 10.1002/14651858.CD006982.pub2.	Neonatal Group	✓
Parmelli E, FlodgrenG, Schaafsma ME, Baillie N, Beyer FR, Eccles MP. The effectiveness of strategies to change organisational culture to improve healthcare performance. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008315. DOI: 10.1002/14651858.CD008315.pub2.	Effective Practice and Organisation of Care Group	✓
Anijeet D, Dolan L, MacEwen CJ. Endonasal versus external dacryocystorhinostomy for nasolacrimal duct obstruction. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007097. DOI: 10.1002/14651858.CD007097.pub2.	Eyes and Vision Group	✓
Brito V, Ciapponi A, Kwong J. Factor Xa inhibitors for acute coronary syndromes. *Cochrane Database of Systematic Reviews 2011*, Issue 1. Art. No.: CD007038. DOI: 10.1002/14651858.CD007038.pub2.	Heart Group	✓
Shi LL, Dong J, NiH, Geng J,Wu T. Felbamate as an add-on therapy for refractory epilepsy. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008295. DOI: 10.1002/14651858.CD008295.pub2.	Epilepsy Group	✓
Hossain M, Alexander P, Burls A, Jobanputra P. Foot orthoses for patellofemoral pain in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008402. DOI: 10.1002/14651858.CD008402.pub2.	Bone, Joint and Muscle Trauma Group	✓
Birch DW, Manouchehri N, Shi X, Hadi G, Karmali S. Heated CO2 with or without humidification for minimally invasive abdominal surgery. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007821. DOI: 10.1002/14651858.CD007821.pub2	Colorectal Cancer Group	✓
NaranbhaiV,AbdoolKarimQ,Meyer-WeitzA. Interventions tomodify sexual risk behaviours for preventing HIV in homeless youth. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007501. DOI: 10.1002/14651858.CD007501.pub	HIV/AIDS Group	✓
Geng J, Dong J, Li Y, Ni H, Jiang K, Shi LL, Wang G. Intravenous immunoglobulins for epilepsy. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD008557. DOI: 10.1002/14651858.CD008557.pub2.	Epilepsy Group	✓
Dasari BVM, McKay D, Gardiner K. Laparoscopic versus Open surgery for small bowel Crohn's disease. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD006956. DOI: 10.1002/14651858.CD006956.pub2	Colorectal Cancer Group	✓
GaitánHG, Reveiz L, Farquhar C. Laparoscopy for the	Menstrual	

management of acute lower abdominal pain in women of childbearing age. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007683. DOI: 10.1002/14651858.CD007683.pub2	Disorders and Subfertility Group	✓
Brooks SC, Bigham BL, Morrison LJ. Mechanical versus manual chest compressions for cardiac arrest. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007260. DOI: 10.1002/14651858.CD007260.pub2.	Heart Group	✓
Gharaibeh A, Savage HI, Scherer RW, Goldberg MF, Lindsley K. Medical interventions for traumatic hyphema. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD005431. DOI: 10.1002/14651858.CD005431.pub2.	Eyes and Vision Group	✓
Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for mid-trimester termination of pregnancy. *Cochrane Database of Systematic Reviews 2011*, Issue 1. Art. No.: CD005216. DOI: 10.1002/14651858.CD005216.pub2.	Fertility Regulation Group	✓
Gordon M, Naidoo K, Thomas AG, Akobeng AK. Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008414. DOI: 10.1002/14651858.CD008414.pub2.	Inflammatory Bowel Disease and Functional Bowel Disorders Group	✓
Gurusamy KS, Pamecha V, Davidson BR. Piggy-back graft for liver transplantation. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008258. DOI: 10.1002/14651858.CD008258.pub2.	Hepato-Biliary Group	✓
Junpeng M, Huang S, Qin S. Progesterone for acute traumatic brain injury. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008409. DOI: 10.1002/14651858.CD008409.pub2.	Injuries Group	✓
Komossa K, Rummel-Kluge C, Schwarz S, Schmid F, Hunger H, Kissling W, Leucht S. Risperidone versus other atypical antipsychotics for schizophrenia. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD006626. DOI: 10.1002/14651858.CD006626.pub2.	Schizophrenia Group	✓
Eke AC, Oragwu C. Sperm washing to prevent HIV transmission from HIV-infected men but allowing conception in sero-discordant couples. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008498. DOI: 10.1002/14651858.CD008498.pub2.	HIV/AIDS Group	X
Taylor F, Ward K, Moore THM, Burke M, Davey Smith G, Casas JP, Ebrahim S. Statins for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD004816. DOI: 10.1002/14651858.CD004816.pub4.	Heart Group	✓

Umoren R, Odey F, Meremikwu MM. Steam inhalation or humidified oxygen for acute bronchiolitis in children up to three years of age. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD006435. DOI: 10.1002/14651858.CD006435.pub2.	Acute Respiratory Infections Group	✓
Al-aqeel S, Al-sabhan J. Strategies for improving adherence to antiepileptic drug treatment in patients with epilepsy. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008312. DOI: 10.1002/14651858.CD008312.pub2.	Epilepsy Group	✓
Kaushik S, Pepas L, Nordin A, Bryant A, Dickinson HO. Surgical interventions for high grade vulval intraepithelial neoplasia. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007928. DOI: 10.1002/14651858.CD007928.pub2.	Gynaecological Cancer Group	✓
Gurusamy KS, Sahay S, Davidson BR. Three dimensional versus two dimensional imaging for laparoscopic cholecystectomy. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD006882. DOI: 10.1002/14651858.CD006882.pub2.	Hepato-Biliary Group	✓
Abdel-Aleem H, Abdel-Aleem MA, Shaaban OM. Tocolysis for management of retained placenta. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD007708. DOI: 10.1002/14651858.CD007708.pub2.	Pregnancy and Childbirth Group	X
Flint A, Webster J. The use of the exit interview to reduce turnover amongst healthcare professionals. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD006620. DOI: 10.1002/14651858.CD006620.pub2.	Effective Practice and Organisation of Care Group	✓
Jagannath VA, Fedorowicz Z, Thaker V, Chang AB. Vitamin K supplementation for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008482. DOI: 10.1002/14651858.CD008482.pub2.	Cystic Fibrosis and Genetic Disorders Group	✓
Mehrholz J, Kugler J, Pohl M. Water-based exercises for improving activities of daily living after stroke. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD008186. DOI: 10.1002/14651858.CD008186.pub2.	Stroke Group	✓

Appendix 2. NHS EED and HEED search strategies

Paley 2011

NHS EED - Economic evaluations
acupuncture OR acupressure OR acupoint* OR electroacupuncture OR electro-acupuncture OR meridian* OR moxibust* OR "traditional chinese medicine" OR "traditional oriental medicine"

HEED - Economic evaluations
AX=acupuncture OR acupressure OR acupoint* OR electroacupuncture OR electro-acupuncture OR meridian* OR moxibust* OR traditional chinese medicine OR traditional oriental medicine

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
(cancer* OR carcino* OR malignan* OR tumor* OR tumour*) AND (pain* OR analges* OR nocicept* OR neuropath*)

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX=(cancer* OR carcino* OR malignan* OR tumor* OR tumour*) AND (pain* OR analges* OR nocicept* OR neuropath*)

Smith 2011

NHS EED - Economic evaluations
acupuncture OR acupressure* OR electroacupuncture OR electro acupuncture OR electro-acupuncture OR meridian* OR mox* OR needling OR acu-point* OR acu point* OR acupoint* OR shu OR shiatsu OR tui na

HEED - Economic evaluations
(AX= acupuncture OR acupressure* OR electroacupuncture OR electro acupuncture OR electro-acupuncture OR meridian* OR mox* OR needling OR acu-point* OR (acu AND point*) OR acupoint* OR shu OR shiatsu OR (tui AND na)) AND (IC= '625')

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
(pain* NEAR period*) OR dysmenorr* OR (menstrua* NEAR cramp*) OR (pelvi* NEAR pain*) OR (period* NEAR cramp*) OR (menstrua* NEAR pain*)

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
IC= '625'

Galaal 2011

NHS EED - Economic evaluations
(uter* OR endometri*) AND (radiotherapy* OR radiation OR chemotherapy* OR drug therap* or antineoplas*)

HEED - Economic evaluations
(AX=(uter* OR endometri*) OR IC=179 OR IC=180 OR IC=181 OR IC=182 OR IC=183 OR IC=184) AND (AX=radiotherapy* OR radiation OR chemotherapy* OR drug* or antineoplas*) AND (AX=neoplasm* OR carcinosarcoma* OR tumo*)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
(uter* OR endometri*) AND (neoplasm* OR carcinosarcoma* OR (mixed AND tumo* and (mullerian or mesodermal)))

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX=(uter* OR endometri*) AND (neoplasm* OR carcinosarcoma* OR (mixed AND tumo* and (mullerian or mesodermal)))

Kuhle 2011

NHS EED - Economic evaluations
((sleep* AND (apnea* OR apnoea* OR hypopn* OR obstruct* OR disorder* OR disturb*)) OR snore* OR snoring*)

HEED - Economic evaluations
(AX= ((sleep* AND (apnea* OR apnoea* OR hypopn* OR obstruct* OR disorder* OR disturb*)) OR snore* OR snoring*) OR IC= 327 OR IC= 770 OR IC = 780) AND (AX= child* OR pediat* OR paediat* OR infan* OR youth* OR toddler* OR adolesc* OR teen* OR boy* OR girl* OR bab* OR preschool* OR pre-school*)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
((sleep* AND (apnea* OR apnoea* OR hypopn* OR obstruct* OR disorder* OR disturb*)) OR snore* OR snoring*)

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= ((sleep* AND (apnea* OR apnoea* OR hypopn* OR obstruct* OR disorder* OR disturb*)) OR snore* OR snoring*)

Showell 2011

NHS EED - Economic evaluations
("male subfertility" OR "In vitro fertilization" OR IVF OR "Intracytoplasmic sperm injection" OR ICSI) AND (antioxidants OR "vitamin e" OR vitamin OR "ascorbic acid" OR zinc OR folate OR selenium OR glutathione OR ubiquinol OR carnitine OR astaxanthin OR "coenzyme Q10" OR lycopene OR Menevit OR carnitine OR "ascorbic acid" OR zinc OR "fatty acids" OR oil OR "fish oils" OR "plant extracts")

HEED - Economic evaluations
(AX = "male subfertility" OR "In vitro fertilization" OR IVF OR "Intracytoplasmic sperm injection" OR ICSI) AND (AX= antioxidants OR "vitamin e" OR vitamin OR "ascorbic acid" OR zinc OR folate OR selenium OR glutathione OR ubiquinol OR carnitine OR astaxanthin OR "coenzyme Q10" OR lycopene OR Menevit OR carnitine OR "ascorbic acid" OR zinc OR "fatty acids" OR oil OR "fish oils" OR "plant extracts")

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
"male subfertility" OR "In vitro fertilization" OR IVF OR "Intracytoplasmic sperm injection" OR ICSI

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX = "male subfertility" OR "In vitro fertilization" OR IVF OR "Intracytoplasmic sperm injection" OR ICSI

Liu 2011

NHS EED - Economic evaluations
(alcohol AND (abuse OR dependen* OR disorder* OR consumption OR withdraw* OR abstinen* OR abstain* OR detox* OR neuropathy OR delirium)) AND (baclofen OR chlorophenyl OR aminobutyric OR butyric OR lioresal)

HEED - Economic evaluations
(AX= alcohol AND (abuse OR dependen* OR disorder* OR consumption OR withdraw* OR abstinen* OR abstain* OR detox* OR neuropathy OR delirium)) AND (AX= baclofen OR chlorophenyl OR aminobutyric OR butyric OR lioresal)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
alcohol AND (abuse OR dependen* OR disorder* OR consumption OR withdraw* OR abstinen* OR abstain* OR detox* OR neuropathy OR delirium)

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= alcohol AND (abuse OR dependen* OR disorder* OR consumption OR withdraw* OR abstinen* OR abstain* OR detox* OR neuropathy OR delirium)

Waseem 2011

NHS EED - Economic evaluations
"botulin* toxin*" OR "clostridium botulin*" OR Botox* OR Dysport* OR oculinum*

HEED - Economic evaluations
AX= (botulin* AND toxin*) OR (clostridium AND botulin*) OR Botox* OR Dysport* OR oculinum*

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
(low* NEAR back* NEAR pain*) OR lbp OR dorsalgia OR backache OR (lumbar NEAR pain) OR coccyx OR coccydynia OR sciatica OR spondylosis OR lumbago OR (back NEAR injur*)

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= (low* AND back* AND pain*) OR lbp OR dorsalgia OR backache OR (lumbar AND pain) OR coccyx OR coccydynia OR sciatica OR spondylosis OR lumbago OR (back AND injur*)

Kamal 2011

NHS EED - Economic evaluations
(cilostazol OR pletal OR pletaal OR OPC-13013 OR OPC 13013 OR OPC-21 OR OPC 21) AND (aspirin OR "acetylsalicylic acid" OR acetyl salicylic acid OR "acetosalicylic acid")

HEED - Economic evaluations
AX= (cilostazol OR pletal OR pletaal OR OPC-13013 OR OPC 13013 OR OPC-21 OR OPC 21)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
tia OR (isch* AND (stroke* OR apoplex* OR cerebral* OR cerebrovasc* OR cva OR attack*)) OR ((brain OR cereb* OR cerebell OR vertebrobasil* OR hemisphere* OR intracran* OR intracerebral OR infratentorial OR supratentorial OR mca OR anterior) AND (isch* OR infarc* OR thrombo* OR emboli* OR occlus* OR hypoxi*))

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= (cilostazol OR pletal OR pletaal OR OPC-13013 OR OPC 13013 OR OPC-21 OR OPC 21)

Aboumarzouk 2011

NHS EED - Economic evaluations
(enterokinetic* NEAR agent*) OR (prokinetic* NEAR substance*) OR Cisapride* OR prepulsid* OR propulsid*

HEED - Economic evaluations
AX= (enterokinetic* AND agent*) OR (prokinetic* AND substance*) OR Cisapride* OR prepulsid* OR propulsid*

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
constipation OR "chronic constipation" OR "colon* inerti*" OR "gastrointestinal* motility" OR "colonic motility" OR "intestinal* dysmotility*" OR "functional* colonic* disease*"

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= constipation OR "chronic constipation" OR (colon* AND inerti*") OR (gastrointestinal* AND motility) OR "colonic motility" OR (intestinal* AND dysmotility*) OR (functional* AND colonic* AND disease*)

Martin 2011

NHS EED - Economic evaluations
"cognitive stimulation" OR "cognitive rehabilitation" OR "cognitive training" OR "cognitive retraining" OR "cognitive re-training" OR "cognitive support" OR "memory function" OR "memory rehabilitation" OR "memory therapy" OR "memory aid*" OR "memory group*" OR "memory training" OR "memory retraining" OR "memory support" OR "memory stimulation" OR "memory strategy" OR "memory management"

HEED - Economic evaluations
AX= "cognitive stimulation" OR "cognitive rehabilitation" OR "cognitive training" OR "cognitive retraining" OR "cognitive re-training" OR "cognitive support" OR "memory function" OR "memory rehabilitation" OR "memory therapy" OR (memory AND aid*) OR (memory AND group*) OR "memory training" OR "memory retraining" OR "memory support" OR "memory stimulation" OR "memory strategy" OR "memory management"

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
N/A – no search terms for 'condition' in published review

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
N/A – no search terms for 'condition' in published review

Morag 2011

NHS EED - Economic evaluations
(premature OR preterm OR (birth AND weight)) AND (periodicity OR "circadian rhythm" OR darkness OR light*)

HEED - Economic evaluations
AX= (premature OR preterm OR (birth AND weight)) AND (periodicity OR "circadian rhythm" OR darkness OR light*)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
N/A – no search terms for 'condition' in published review

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
N/A – no search terms for 'condition' in published review

Parmelli 2011

NHS EED - Economic evaluations
(organi* NEAR cultur*) OR (corporate NEAR culture*) OR (work* NEAR culture*) OR (organi* NEAR ethos) OR (organi* NEAR climate*)

HEED - Economic evaluations
AX= (organi* AND cultur*) OR (corporate AND culture*) OR (work* AND culture*) OR (organi* AND ethos) OR (organi* AND climate*)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
N/A – no condition

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
N/A – no condition

Anijeet 2011

NHS EED - Economic evaluations
dacryocystorhinostom* OR ((endonasal OR external) AND DCR) OR (lacrimal NEAR obstruct*)

HEED - Economic evaluations
AX= dacryocystorhinostom* OR ((endonasal OR external) AND DCR) OR (lacrimal AND obstruct*)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
lacrimal NEAR obstruct*

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= lacrimal AND obstruct*

Brito 2011

NHS EED - Economic evaluations
fondaparin* OR idraparinux OR arixtra OR otamixaban OR ((xa OR 10a) AND (inhibit* OR antagonist* OR block*)) OR ("factor x" NEAR inhibit*) OR (fxa NEAR inhibitor*) OR "vaso flux" OR razaxaban OR "dx 9065"

HEED - Economic evaluations
AX= fondaparin* OR idraparinux OR arixtra OR otamixaban OR ((xa OR 10a) AND (inhibit* OR antagonist* OR block*)) OR ("factor x" AND inhibit*) OR (fxa AND inhibitor*) OR "vaso flux" OR razaxaban OR "dx 9065"

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
"myocardial ischemi*" OR angina OR "myocardial infarct*" OR "heart infarct*" OR "acute coronar*" OR "coronary syndrome*" OR preinfarct* OR "pre infarct*" OR stemi OR nonstemi OR non-stemi OR nstemi OR ACS

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
(AX= (myocardial AND ischemi*) OR angina OR (myocardial AND infarct*) OR (heart AND infarct*) OR (acute AND coronar*) OR (coronary AND syndrome*) OR preinfarct* OR (pre AND infarct*) OR stemi OR nonstemi OR non-stemi OR nstemi OR ACS) AND
EE= (Cost AND of AND illness)

Shi 2011

NHS EED - Economic evaluations
felbamate OR taloxa* OR felbatol OR ADD-03055 OR W-554

HEED - Economic evaluations
AX= felbamate OR taloxa* OR felbatol OR ADD-03055 OR W-554

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
epilep* OR seizure* OR convulsion*

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= epilep* OR seizure* OR convulsion*

Hossain 2011

NHS EED - Economic evaluations
(orthos* OR orthotic* OR insert*) AND (foot OR feet OR shoe*)

HEED - Economic evaluations
AX = (orthos* OR orthotic* OR insert*) AND (foot OR feet OR shoe*)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
"anterior knee pain" OR ((knee* OR patell* OR femoro* OR retropatell*) AND (pain OR syndrome OR dysfunction OR chondromalac* OR chondropath*)) OR (("lateral compression" OR "lateral facet" OR "lateral pressure" OR "odd facet") AND syndrome)

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= "anterior knee pain" OR ((knee* OR patell* OR femoro* OR retropatell*) AND (pain OR syndrome OR dysfunction OR chondromalac* OR chondropath*)) OR (("lateral compression" OR "lateral facet" OR "lateral pressure" OR "odd facet") AND syndrome)

Birch 2011

NHS EED - Economic evaluations
(gas* OR "carbon dioxide" OR co2 OR "nitrous oxide" OR n2o OR helium OR argon OR "laughing gas") AND (surger* OR procedure* OR endoscop* OR laparoscop* OR peritineoscop*) AND (heat* OR temperature* OR warm* OR isotherm*)

HEED - Economic evaluations
AX= (gas* OR "carbon dioxide" OR co2 OR "nitrous oxide" OR n2o OR helium OR argon OR "laughing gas") AND (surger* OR procedure* OR endoscop* OR laparoscop* OR peritineoscop*) AND (heat* OR temperature* OR warm* OR isotherm*)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
N/A – no search terms for 'condition' in published review

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
N/A – no search terms for 'condition' in published review

Naranbhai 2011

NHS EED - Economic evaluations
(risk* AND (reduc* OR behav* OR lifestyle* OR sexual*)) AND ((homeless* OR street*) AND (youth* OR child*))

HEED - Economic evaluations
AX= (risk* AND (reduc* OR behav* OR lifestyle* OR sexual*)) AND ((homeless* OR street*) AND (youth* OR child*))

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
((homeless* OR street*) AND (youth* OR child*)) AND (((human OR acquired) AND immun*) OR hiv*)

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= ((homeless* OR street*) AND (youth* OR child*)) AND (((human OR acquired) AND immun*) OR hiv*)

Geng 2011

NHS EED - Economic evaluations
(intravenous immu* OR IV immunoglobulin* OR IVIG OR "intravenous IG" OR intraglobi* OR intravenous antibod* OR IV antibod*) AND (epilep* OR seizu* OR convuls* OR "Lennox Gastaut" OR "infantile spasm")

HEED - Economic evaluations
AX= ((intravenous AND immu*) OR (IV AND immunoglobulin*) OR IVIG OR "intravenous IG" OR intraglobi* OR (intravenous AND antibod*) OR (IV AND antibod*)) AND (epilep* OR seizu* OR convuls* OR "Lennox Gastaut" OR "infantile spasm")

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
epilep* OR seizu* OR convuls* OR "Lennox Gastaut" OR "infantile spasm"

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= epilep* OR seizu* OR convuls* OR "Lennox Gastaut" OR "infantile spasm"

Dasari 2011

NHS EED - Economic evaluations
laparoscop* AND (crohn* NEAR disease*)

HEED - Economic evaluations
AX= laparoscop* AND (crohn* AND disease*)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
(crohn* NEAR disease*)

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= crohn* AND disease*

Gaitán 2011

NHS EED - Economic evaluations
laparoscop* AND (append* OR "PID" OR ((abdomen OR abdomin* OR pelvic) AND pain) OR (pelvic NEAR disease) OR (ovar* NEAR cyst*))

HEED - Economic evaluations
AX= laparoscop* AND (append* OR "PID" OR ((abdomen OR abdomin* OR pelvic) AND pain) OR (pelvic AND disease) OR (ovar* AND cyst*))

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
(append* OR "PID" OR ((abdomen OR abdomin* OR pelvic) AND pain) OR (pelvic NEAR disease) OR (ovar* NEAR cyst*))

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= (append* OR "PID" OR ((abdomen OR abdomin* OR pelvic) AND pain) OR (pelvic AND disease) OR (ovar* AND cyst*))

Brooks 2011

NHS EED - Economic evaluations
("cpr" OR resuscitat* OR heart massage OR cardiac massage OR chest compression) AND (piston OR autopulse OR auto-pulse OR thumper OR pneumatic OR lucas OR hands-free OR load distributing OR vest OR mechanical OR automat* OR device OR machine)

HEED - Economic evaluations
AX= ("cpr" OR resuscitat* OR heart massage OR cardiac massage OR chest compression) AND (piston OR autopulse OR auto-pulse OR thumper OR pneumatic OR lucas OR hands-free OR load distributing OR vest OR mechanical OR automat* OR device OR machine)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
cardiac arrest OR heart arrest OR cardiopulmonary arrest OR (sudden NEAR death)

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= cardiac arrest OR heart arrest OR cardiopulmonary arrest OR (sudden AND death)

Gharaibeh 2011

NHS EED - Economic evaluations
hyphem* or hyphaem*

HEED - Economic evaluations
AX= hyphem* or hyphaem*

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
hyphem* or hyphaem*

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= hyphem* or hyphaem*

Wildschut 2011

NHS EED - Economic evaluations
abort* AND (mifepristone* OR misoprostol* OR methotrexate* OR dinoprost* OR carboprost* OR sulprostone* OR gemeprost* OR meteneprost* OR epostane* OR oxytocin* OR "RU 486" OR mifegyne* OR "ethacridine lactate")

HEED - Economic evaluations
AX= abort* AND (mifepristone* OR misoprostol* OR methotrexate* OR dinoprost* OR carboprost* OR sulprostone* OR gemeprost* OR meteneprost* OR epostane* OR oxytocin* OR "RU 486" OR mifegyne* OR "ethacridine lactate")

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
abort* AND "second trimester"

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= abort* AND "second trimester"

Gordon 2011

NHS EED - Economic evaluations
("aminosalicylic acid" OR aminosalicylate OR "5-ASA" OR mesalazine OR mesalamine OR olsalazine OR balsalazide) AND (surgic* OR post-surg* OR postoperative OR post-operative OR resection OR operation)

HEED - Economic evaluations
AX= ("aminosalicylic acid" OR aminosalicylate OR "5-ASA" OR mesalazine OR mesalamine OR olsalazine OR balsalazide) AND (surgic* OR post-surg* OR postoperative OR post-operative OR resection OR operation)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
(crohn* NEAR disease) OR "regional enteritis" OR ileitis OR "inflammatory bowel disease"

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= (crohn* AND disease) OR "regional enteritis" OR ileitis OR "inflammatory bowel disease"

Gurusamy 2011a

NHS EED - Economic evaluations
(piggy* OR cavo*) AND ((liver OR hepatic) AND (transplant* OR graft*))

HEED - Economic evaluations
AX= (piggy* OR cavo*) AND ((liver OR hepatic) AND (transplant* OR graft*))

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
N/A – no search terms for 'condition' in published review

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
N/A – no search terms for 'condition' in published review

Junpeng 2011

NHS EED - Economic evaluations
((head OR brain* OR cranial OR cerebral OR intra-cranial OR inter-cranial) AND (injur* OR trauma* OR damag* OR wound* OR fracture* OR contusion* OR polytrauma* OR haematoma* OR hematoma* OR haemorrhag* OR hemorrhag* OR bleed*)) AND (progest* OR estrogen* OR gestagen* OR Gonadal Steroid Hormones)

HEED - Economic evaluations
AX= ((head OR brain* OR cranial OR cerebral OR intra-cranial OR inter-cranial) AND (injur* OR trauma* OR damag* OR wound* OR fracture* OR contusion* OR polytrauma* OR haematoma* OR hematoma* OR haemorrhag* OR hemorrhag* OR bleed*)) AND (progest* OR estrogen* OR gestagen* OR "Gonadal Steroid Hormones")

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
((head OR brain* OR cranial OR cerebral OR intra-cranial OR inter-cranial) AND (injur* OR trauma* OR damag* OR wound* OR fracture* OR contusion* OR polytrauma* OR haematoma* OR hematoma* OR haemorrhag* OR hemorrhag* OR bleed*))

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= ((head OR brain* OR cranial OR cerebral OR intra-cranial OR inter-cranial) AND

(injur* OR trauma* OR damag* OR wound* OR fracture* OR contusion* OR polytrauma* OR haematoma* OR hematoma* OR haemorrhag* OR hemorrhag* OR bleed*))

Komossa 2011

NHS EED - Economic evaluations
ziprasidon* AND (amisulprid* OR aripiprazol* OR clozapin* OR olanzapin* OR quetiapin* OR sertindol* OR risperidon* OR zotepin*)

HEED - Economic evaluations
AX= ziprasidon* AND (amisulprid* OR aripiprazol* OR clozapin* OR olanzapin* OR quetiapin* OR sertindol* OR risperidon* OR zotepin*)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
schizophren*

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= schizophren* AND EE= (cost AND of AND illness)

Taylor 2011

NHS EED - Economic evaluations
(statin* OR atorvastatin* OR cerivastatin* OR fluvastatin* OR lovastatin* OR pravastatin* OR simvastatin* OR lipitor OR baycol OR lescol OR mevacor OR altocor OR pravachol OR lipostat OR zocor OR mevinolin OR compactin OR fluindostatin OR rosuvastatin) AND (cardiovascular OR "heart disease*" OR "coronary disease*" OR angina OR "heart failure" OR "cardiac failure" OR hyperlipid* OR hypercholestorol* OR cholestorol*)

HEED - Economic evaluations
AX= (statin* OR atorvastatin* OR cerivastatin* OR fluvastatin* OR lovastatin* OR pravastatin* OR simvastatin* OR lipitor OR baycol OR lescol OR mevacor OR altocor OR pravachol OR lipostat OR zocor OR mevinolin OR compactin OR fluindostatin OR rosuvastatin) AND (cardiovascular OR (disease* AND (heart OR coronary)) OR angina OR "heart failure" OR "cardiac failure" OR hyperlipid* OR hypercholestorol* OR cholestorol*)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
(cardiovascular OR "heart disease*" OR "coronary disease*" OR angina OR "heart failure" OR "cardiac failure" OR hyperlipid* OR hypercholestorol* OR cholestorol*) AND (cost:ty OR review:ty)

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= (cardiovascular OR (disease* AND (heart OR coronary)) OR angina OR "heart failure" OR "cardiac failure" OR hyperlipid* OR hypercholestorol* OR cholestorol*) AND EE= (cost AND of AND illness)

Umoren 2011

NHS EED - Economic evaluations
(bronchiolit* OR "respiratory syncytial virus*" OR "rsv" OR flu OR influenza* OR parainfluenza* OR adenovir*) AND ("respiratory therapy" OR "oxygen inhalation therapy" OR steam* OR mist* OR ((oxygen* OR o2 OR air OR water OR burn*) AND (inhal* OR nebuli* OR atomi* OR humidify* OR vapour* OR vapor*)))

HEED - Economic evaluations
AX= (bronchiolit* OR (respiratory AND syncytial AND virus) OR "rsv" OR flu OR influenza* OR parainfluenza* OR adenovir*) AND ("respiratory therapy" OR "oxygen inhalation therapy" OR steam* OR mist* OR ((oxygen* OR o2 OR air OR water OR burn*) AND (inhal* OR nebuli* OR atomi* OR humidify* OR vapour* OR vapor*)))

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
(bronchiolit* or "respiratory syncytial virus*" OR "rsv" OR flu OR influenza* OR parainfluenza* OR adenovir*)

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= (bronchiolit* OR (respiratory AND syncytial AND virus) OR "rsv" OR flu OR influenza* OR parainfluenza* OR adenovir*) AND EE= (cost AND of AND illness)

Al-aqee 2011

NHS EED - Economic evaluations
((patient NEAR complian*) OR (patient NEAR adheren*)) AND (epilep* OR seizure* OR convulsion* OR antiepilep*)

HEED - Economic evaluations
AX= ((patient AND complian*) OR (patient AND adheren*)) AND (epilep* OR seizure* OR convulsion* OR antiepilep*)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
(epilep* OR seizure* OR convulsion* OR antiepilep*)

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= (epilep* OR seizure* OR convulsion* OR antiepilep*)

Kaushik 2011

NHS EED - Economic evaluations
VIN OR VIN2 OR VIN3 OR (vulva* AND "intraepithelial neoplasia") OR (vulva* AND (pre-cancer* OR precancer* OR dysplasia OR unifocal OR multifocal OR "carcinoma in situ"))

HEED - Economic evaluations
AX= VIN OR VIN2 OR VIN3 OR (vulva* AND (intraepithelial OR pre-cancer* OR precancer* OR dysplasia OR unifocal OR multifocal)) OR "carcinoma in situ"

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
VIN OR VIN2 OR VIN3 OR (vulva* AND "intraepithelial neoplasia") OR (vulva* AND (pre-cancer* OR precancer* OR dysplasia OR unifocal OR multifocal OR "carcinoma in situ"))

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= VIN OR VIN2 OR VIN3 OR (vulva* AND (intraepithelial OR pre-cancer* OR precancer* OR dysplasia OR unifocal OR multifocal)) OR "carcinoma in situ"

Gurusamy 2011b

NHS EED - Economic evaluations
((laparoscop* OR coelioscop* OR celioscop* OR peritoneoscop*) AND (cholecystectom* AND ((two OR three) AND (dimension* OR imag*))))

HEED - Economic evaluations
AX= ((laparoscop* OR coelioscop* OR celioscop* OR peritoneoscop*) AND (cholecystectom* AND ((two OR three) AND (dimension* OR imag*))))

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
gallston* OR cholecystolithiasis

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= gallston* OR cholecystolithiasis

Flint 2011

NHS EED - Economic evaluations
(turnover OR attrition) AND (interview* OR feedback OR organisation* OR organization*)

HEED - Economic evaluations
AX= (turnover OR attrition) AND (interview* OR feedback OR organisation* OR organization*)

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
(turnover OR attrition) AND (organisation* OR organization*)

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= (turnover OR attrition) AND (organisation* OR organization*)

Jagannath 2011

NHS EED - Economic evaluations
vitamin K

HEED - Economic evaluations
AX= vitamin K

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
N/A – no search terms for 'condition' in published review

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
N/A – no search terms for 'condition' in published review

Mehrholz 2011

NHS EED - Economic evaluations
(water OR seawater OR aqua* OR hydrokinetic* OR hydro-kinetic* OR pool OR swim*) AND (exercise* OR fitness OR physiotherapy* OR activit* OR aerobic OR training OR therap* OR rehabilitation OR treadmill OR walking OR gymnastic* OR calisthenic* OR "Ai Chi" OR Halliwick OR hydrotherapy* OR whirlpool* OR bath*) AND (stroke* OR cva OR poststroke OR post-stroke OR infarct* or ischemi* OR ischaemi* OR thrombo* OR emboli* OR apoplexy OR haemorrhage OR hemorrhage OR haematoma OR hematoma or bleed* OR hempar* OR hemipleg* OR "brain injur*")

HEED - Economic evaluations
AX= (water OR seawater OR aqua* OR hydrokinetic* OR hydro-kinetic* OR pool OR

swim*) AND (exercise* OR fitness OR physiotherapy* OR activit* OR aerobic OR training OR therap* OR rehabilitation OR treadmill OR walking OR gymnastic* OR calisthenic* OR "Ai Chi" OR Halliwick OR hydrotherapy* OR whirlpool* OR bath*) AND (stroke* OR cva OR poststroke OR post-stroke OR infarct* or ischemi* OR ischaemi* OR thrombo* OR emboli* OR apoplexy OR haemorrhage OR hemorrhage OR haematoma OR hematoma or bleed* OR hempar* OR hemipleg* OR (brain AND injur*))

NHS EED – Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
stroke* OR cva OR poststroke OR post-stroke OR hempar* OR hemipleg* OR "brain injur*" OR ((cereb* OR brain* OR vertebrobasiliar OR subarachnoid) AND (infarct* or ischemi* OR ischaemi* OR thrombo* OR emboli* OR apoplexy OR haemorrhage OR hemorrhage OR haematoma OR hematoma or bleed*))

HEED - Economic analyses: 'economic burden of condition' and/or 'cost-of-illness'
AX= (stroke* OR cva OR poststroke OR post-stroke OR infarct* or ischemi* OR ischaemi* OR thrombo* OR emboli* OR apoplexy OR haemorrhage OR hemorrhage OR haematoma OR hematoma or bleed* OR hempar* OR hemipleg* OR (brain AND injur*)) AND EE= (cost AND illness)

Appendix 3. Tabulated results

Table A3.1. Economic evaluations assessed as 'potentially eligible' based on initial screening ('Screen 1' - NHS EED and/or HEED record only), by record source

First author/ year	*Total records*	*Record unique to NHS EED*	*Record unique to HEED*	*Duplicate records*
Paley 2011	0	-	-	-
Smith 2011	1	0	0	1
Galaal 2011	1	1	0	0
Kuhle 2011	0	-	-	-
Showell 2011	0	-	-	-
Liu 2011	0	-	-	-
Waseem 2011	0	-	-	-
Kamal 2011	1	0	0	1
Aboumarzouk 2011	0	-	-	-
Martin 2011	3	1	2	0
Morag 2011	0	-	-	-
Parmelli 2011	0	-	-	-
Anijeet 2011	1	1	0	0
Brito 2011	3	0	0	3
Shi 2011	0	-	-	-
Hossain 2011	0	-	-	-
Birch 2011	0	-	-	-
Naranbhai 2011	0	-	-	-
Geng 2011	0	-	-	-
Dasari 2011	7	1	2	4
Gaitán 2011	3	1	0	2
Brooks 2011	0	-	-	-
Gharaibeh 2011	0	-	-	-
Wildschut 2011	5	2	3	0
Gordon 2011	0	-	-	-
Gurusamy 2011a	0	-	-	-
Junpeng 2011	0	-	-	-
Komossa 2011	12	2	4	6
Taylor 2011	32	3	9	19
Umoren 2011	0	-	-	-
Al-aqee 2011	0	-	-	-
Kaushik 2011	0	-	-	-
Gurusamy 2011b	0	-	-	-
Flint 2011	0	-	-	-
Jagannath 2011	0	-	-	-
Mehrholz 2011	0	-	-	-

Table A3.2. Economic evaluations assessed as 'eligible' based on second round of screening ('Screen 2' - NHS EED and/or HEED record and article abstract and/or full-text if required), by record source

First author/ year	*Total records*	*Record unique to NHS EED*	*Record unique to HEED*	*Duplicate records*
Paley 2011	0	-	-	-
Smith 2011	1	0	0	1
Galaal 2011	0	-	-	-
Kuhle 2011	0	-	-	-
Showell 2011	0	-	-	-
Liu 2011	0	-	-	-
Waseem 2011	0	-	-	-
Kamal 2011	1	0	0	1
Aboumarzouk 2011	0	-	-	-
Martin 2011	1	0	1	0
Morag 2011	0	-	-	-
Parmelli 2011	0	-	-	-
Anijeet 2011	1	1	0	0
Brito 2011	3	0	0	3
Shi 2011	0	-	-	-
Hossain 2011	0	-	-	-
Birch 2011	0	-	-	-
Naranbhai 2011	0	-	-	-
Geng 2011	0	-	-	-
Dasari 2011	6	1	2	3
Gaitán 2011	2	1	0	1
Brooks 2011	0	-	-	-
Gharaibeh 2011	0	-	-	-
Wildschut 2011	1	1	0	0
Gordon 2011	0	-	-	-
Gurusamy 2011a	0	-	-	-
Junpeng 2011	0	-	-	-
Komossa 2011	11	1	4	6
Taylor 2011	24	1	8	15
Umoren 2011	0	-	-	-
Al-aqee 2011	0	-	-	-
Kaushik 2011	0	-	-	-
Gurusamy 2011b	0	-	-	-
Flint 2011	0	-	-	-
Jagannath 2011	0	-	-	-
Mehrholz 2011	0	-	-	-

Table A3.3. Economic evaluations assessed as 'eligible' based on second round of screening ('Screen 2' - NHS EED and/or HEED record and article abstract and/or full-text if required), by economic evaluation type

First author/ year	*Total records*	*CEA (Empirical study)*	*CEA (Decision model)*	*CEA (Empirical study and Decision model)*	*CEA (Cost consequences - Empirical study)*	*CEA (Cost consequences - Decision model)*	*CUA (Empirical study)*	*CUA (Decision model)*	*CBA (Any design)*	*Cost analysis*	*Not classified*
Paley 2011	0	-	-	-	-	-	-	-	-	-	-
Smith 2011	1	0	0	0	0	0	1	0	0	0	0
Galaal 2011	0	-	-	-	-	-	-	-	-	-	-
Kuhle 2011	0	-	-	-	-	-	-	-	-	-	-
Showell 2011	0	-	-	-	-	-	-	-	-	-	-
Liu 2011	0	-	-	-	-	-	-	-	-	-	-
Waseem 2011	0	-	-	-	-	-	-	-	-	-	-
Kamal 2011	1	0	0	0	0	0	0	1	0	0	0
Aboumarzouk 2011	0	-	-	-	-	-	-	-	-	-	-
Martin 2011	1	0	0	0	0	0	0	0	0	0	1
Morag 2011	0	-	-	-	-	-	-	-	-	-	-
Parmelli 2011	0	-	-	-	-	-	-	-	-	-	-
Anijeet 2011	1	0	0	0	0	0	0	0	0	1	0
Brito 2011	3	0	1	0	0	0	0	2	0	0	0
Shi 2011	0	-	-	-	-	-	-	-	-	-	-
Hossain 2011	0	-	-	-	-	-	-	-	-	-	-
Birch 2011	0	-	-	-	-	-	-	-	-	-	-
Naranbhai 2011	0	-	-	-	-	-	-	-	-	-	-
Geng 2011	0	-	-	-	-	-	-	-	-	-	-
Dasari 2011	6	0	0	0	5	0	0	0	0	1	0
Gaitán 2011	2	2	0	0	0	0	0	0	0	0	0
Brooks 2011	0	-	-	-	-	-	-	-	-	-	-
Gharaibeh 2011	0	-	-	-	-	-	-	-	-	-	-
Wildschut 2011	1	1	0	0	0	0	0	0	0	0	0
Gordon 2011	0	-	-	-	-	-	-	-	-	-	-
Gurusamy 2011a	0	-	-	-	-	-	-	-	-	-	-
Junpeng 2011	0	-	-	-	-	-	-	-	-	-	-

Komossa 2011	11	0	5	0	0	1	0	3	0	1	1
Taylor 2011	24	5	6	1	0	1	1	7	0	0	2
Umoren 2011	0	-	-	-	-	-	-	-	-	-	-
Al-aqee 2011	0	-	-	-	-	-	-	-	-	-	-
Kaushik 2011	0	-	-	-	-	-	-	-	-	-	-
Gurusamy 2011b	0	-	-	-	-	-	-	-	-	-	-
Flint 2011	0	-	-	-	-	-	-	-	-	-	-
Jagannath 2011	0	-	-	-	-	-	-	-	-	-	-
Mehrholz 2011	0	-	-	-	-	-	-	-	-	-	-
Total (% of total)	51 (100)	8 (16)	12 (24)	1 (2)	4 (8)	2 (4)	2 (4)	13 (25)	0 (0)	3 (6)	4 (8)

Key

CEA: Cost-effectiveness analysis

CUA: Cost-utility analysis

CBA: Cost-benefit analysis

Table A3.4. Economic evaluations assessed as 'eligible' based on second round of screening ('Screen 2' - NHS EED and/or HEED record and article abstract and/or full-text if required), by basis for classification

First author/ year	*Total records*	*Classified based on NHS EED/ HEED record alone*	*Classified based on article abstract/full-text*	*Not classified*
Paley 2011	0	-	-	-
Smith 2011	1	1	0	0
Galaal 2011	0	-	-	-
Kuhle 2011	0	-	-	-
Showell 2011	0	-	-	-
Liu 2011	0	-	-	-
Waseem 2011	0	-	-	-
Kamal 2011	1	1	0	0
Aboumarzouk 2011	0	-	-	-
Martin 2011	1	0	0	1
Morag 2011	0	-	-	-
Parmelli 2011	0	-	-	-
Anijeet 2011	1	0	1	0
Brito 2011	3	1	2	0
Shi 2011	0	-	-	-
Hossain 2011	0	-	-	-
Birch 2011	0	-	-	-
Naranbhai 2011	0	-	-	-
Geng 2011	0	-	-	-
Dasari 2011	6	4	2	0
Gaitán 2011	2	2	0	0
Brooks 2011	0	-	-	-
Gharaibeh 2011	0	-	-	-
Wildschut 2011	1	1	0	0
Gordon 2011	0	-	-	-
Gurusamy 2011a	0	-	-	-
Junpeng 2011	0	-	-	-
Komossa 2011	11	9	1	1
Taylor 2011	24	20	2	2
Umoren 2011	0	-	-	-
Al-aqee 2011	0	-	-	-
Kaushik 2011	0	-	-	-
Gurusamy 2011b	0	-	-	-
Flint 2011	0	-	-	-
Jagannath 2011	0	-	-	-
Mehrholz 2011	0	-	-	-
Total (% of total)	51 (100)	40 (78)	8 (16)	4 (8)

Table A3.5. Economic analyses ('economic burden of condition' and/or 'cost-of-illness') assessed as 'potentially eligible' based on initial screening ('Screen 1' - NHS EED and/or HEED record only), by record source

First author/ year	*Total records*	*Record unique to NHS EED*	*Record unique to HEED*	*Duplicate records*
Paley 2011	2	1	0	1
Smith 2011	2	0	2	0
Galaal 2011	0	-	-	-
Kuhle 2011	10	4	2	4
Showell 2011	8	3	3	2
Liu 2011	40	8	29	3
Waseem 2011	28	12	9	7
Kamal 2011	21	5	9	7
Aboumarzouk 2011	6	3	0	3
Anijeet 2011	0	-	-	-
Brito 2011	17	15	1	1
Shi 2011	7	3	0	4
Hossain 2011	0	-	-	-
Naranbhai 2011	0	-	-	-
Geng 2011	53	9	24	20
Dasari 2011	16	0	8	8
Gaitán 2011	4	2	1	1
Brooks 2011	5	3	2	0
Gharaibeh 2011	0	-	-	-
Wildschut 2011	0	-	-	-
Gordon 2011	21	1	11	9
Junpeng 2011	21	9	8	4
Komossa 2011	70	43	16	11
Taylor 2011	24	12	5	7
Umoren 2011	4	4	0	0
Al-aqee 2011	55	9	24	22
Kaushik 2011	0	-	-	-
Gurusamy 2011b	0	-	-	-
Flint 2011	0	-	-	-
Mehrholz 2011	73	51	9	13

Table A3.6. Economic analyses ('economic burden of condition' and/or 'cost-of-illness') assessed as eligible' based on second round of screening ('Screen 2' - NHS EED and/or HEED record and article abstract and/or full-text if required), by record source - selected reviews only

First author/ year	*Total records*	*Record unique to NHS EED*	*Record unique to HEED*	*Duplicate records*
Kamal 2011	19	4	9	6
Brito 2011	17	15	1	1
Dasari 2011	16	0	8	8
Wildschut 2011	0	-	-	-
Komossa 2011	66	39	16	11

Table A3.7. Economic analyses ('economic burden of condition' and/or 'cost-of-illness') assessed as assessed as eligible' based on second round of screening ('Screen 2' - NHS EED and/or HEED record and article abstract and/or full-text if required), by analysis type - selected reviews only

First author/ year	*Total records*	*Cost-of-illness (Applied study)*	*Review of applied cost-of-illness analyses*	*Cost-of-illness and CEA (Cost-consequences)*	*Cost-of-illness and Econometric analysis*	*Not classified*
Kamal 2011	19	12	4	2	0	1
Brito 2011	17	12	3	0	0	2
Dasari 2011	16	7	5	1	0	3
Wildschut 2011	0	-	-	-	0	-
Komossa 2011	65	27	18	1	11	8
Total (% of total)	117 (100)	58 (50)	30 (26)	4 (3)	11 (9)	14 (12)

Key
CEA: Cost-effectiveness analysis

Table A3.8. Economic analyses ('economic burden of condition' and/or 'cost-of-illness') assessed as assessed as eligible' based on second round of screening ('Screen 2' - NHS EED and/or HEED record and article abstract and/or full-text if required), by basis for classification - selected reviews only

First author/ year	*Total records*	*Classified based on NHS EED/ HEED record alone*	*Classified based on article abstract/ full-text*	*Not classified*
Kamal 2011	19	12	6	1
Brito 2011	17	2	13	2
Dasari 2011	16	11	2	3
Wildschut 2011	0	-	-	-
Komossa 2011	65	31	26	8
Total (% of total)	117 (100)	56 (48)	47 (40)	14 (12)

Appendix 4. References lists of records/articles assessed as eligible based on second round of screening - selected reviews only

Table A4.1. Economic evaluations: format availability and use to inform development of economic commentary

Key
A: NHS EED structured abstract record
B: NHS EED citation only record
C: HEED field-coded abstract record
D: HEED citation only record
E: Article abstract
F: Article full-text
G: Used to inform development of economic commentary

Kamal 2011							
Citation	*A*	*B*	*C*	*D*	*E*	*F*	*G*
Inoue T, Kobayashi M, Uetsuka Y, Uchiyama S. Pharmacoeconomic analysis of cilostazol for the secondary prevention of cerebral infarction. *Circulation Journal* 2006; 70(4): 453-458.	✓		✓		✓	✓	✓
Brito 2011							
Citation	*A*	*B*	*C*	*D*	*E*	*F*	*G*
Latour-Perez J, De-Miguel-Balsa E. Cost effectiveness of fondaparinux in non-ST-elevation acute coronary syndrome. *Pharmacoeconomics* 2009; 27(7): 585-595.		✓	✓		✓	✓	✓
Maxwell CB, Holdford DA, Crouch MA, Patel DA. Cost-effectiveness analysis of anticoagulation strategies in non-ST-elevation acute coronary syndromes. *Annals of Pharmacotherapy* 2009; 43(4): 586-595.	✓		✓		✓		✓
Sculpher M J, Lozano-Ortega G, Sambrook J, Palmer S, Ormanidhi O, Bakhai A, Flather M, Steg P G, Mehta S R, Weintraub W. Fondaparinux versus Enoxaparin in non-ST-elevation acute coronary syndromes: short-term cost and long-term cost-effectiveness		✓	✓		✓	✓	✓

using data from the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (OASIS-5) trial. *American Heart Journal* 2009; 157(5): 845-852.							
Dasari 2011							
Citation	*A*	*B*	*C*	*D*	*E*	*F*	*G*
Duepree H J, Senagore A J, Delaney C P, Brady K M, Fazio V W. Advantages of laparoscopic resection for ileocecal Crohn's disease. *Diseases of the Colon and Rectum* 2002; 45(5): 605-610	✓			✓	✓	✓	✓
Maartense S, Dunker M S, Slors J F, Cuesta M A, Pierik E G, Gouma D J, Hommes D W, Sprangers M A, Bemelman W A. Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial. *Annals of Surgery* 2006; 243(2): 143-149	✓		✓		✓	✓	✓
Msika S, Iannelli A, Deroide G, Jouet P, Soule J-C, Kianmanesh R, Perez N, Flamant Y, Fingerhut A, Hay J-M. Can laparoscopy reduce hospital stay in the treatment of Crohn's disease? *Diseases of the Colon and Rectum* 2001; 44(11):1661-1666.			✓		✓	✓	✓
Scarpa M, Ruffolo C, Bassi D, Boetto R, D'Inca R, Buda A, Sturniolo G C, Angriman I. Intestinal surgery for Crohn's disease: predictors of recovery, quality of life, and costs. *Journal of Gastrointestinal Surgery* 2009; 13: 2128-2135.			✓		✓	✓	✓
Shore G, Gonzalez Q H, Bondora A, Vickers S M. Laparoscopic vs conventional ileocolectomy for primary Crohn disease. *Archives of Surgery* 2003; 138(1): 76-79.		✓			✓	✓	✓
Young-Fadok T M, Long K H, McConnell E J, Rey G G, Cabanela R L. Advantages of laparoscopic resection for ileocolic Crohn's disease: improved outcomes and reduced costs. *Surgical Endoscopy - Ultrasound and Interventional Techniques* 2001; 15(5): 450-454.	✓		✓		✓	✓	✓
Wildschut 2011							
Citation	*A*	*B*	*C*	*D*	*E*	*F*	*G*
Ngai S W, Tang O S, Ho P C. Randomized comparison of vaginal (200 µg evrey 3 h) and oral (400 µg every 3 h) misoprostol when combined with mifepristone in termination of second trimester pregnancy. *Human Reproduction* 2000; 15: 2205-2208.			✓		✓	✓	✓
Komossa 2011							

Citation	*A*	*B*	*C*	*D*	*E*	*F*	*G*
Beard A M, Maciver F, Clouth J, Ruther E. A decision model to compare health care costs of olanzapine and risperidone treatment of schizophrenia in Germany. *European Journal of Health Economics* 2006; 7: 165-172.	✓				✓	✓	✓
Edwards N C, Locklear J C, Rupnow M F, Diamond R J. Cost effectiveness of long-acting risperidone injection versus alternative antipsychotic agents in patients with schizophrenia in the USA. *Pharmacoeconomics* 2005; 23(Supplement 1): 75-89.	✓		✓		✓	✓	✓
Edwards NC, Pesa J, Meletiche DM, Engelhart L, Thompson AK, Sherr J, Dirani R. One-year clinical and economic consequences of oral atypical antipsychotics in the treatment of schizophrenia. *Current Medical Research and Opinion* 2008; 24(12): 3341-3355.	✓		✓		✓	✓	✓
Furiak N M, Ascher-Svanum H, Klein R W, Smolen L J, Lawson A H, Conley R R, Culler S D. Cost-effectiveness model comparing olanzapine and other oral atypical antipsychotics in the treatment of schizophrenia in the United States. *Cost Effectiveness and Resource Allocation* 2009; 7:4.			✓		✓	✓	✓
Geitona M, Kousoulakou H, Ollandezos M, Athanasakis K, Papanicolaou S, Kyriopoulos I. Costs and effects of paliperidone extended release compared with alternative oral antipsychotic agents in patients with schizophrenia in Greece: a cost effectiveness study. *Annals of General Psychiatry* 2008; 7:16.	✓		✓		✓	✓	✓
Jerrell J M, McIntyre R S. Health-care costs of pediatric clients developing adverse events during treatment with antipsychotics. *Value in Health* 2009; 12(5):716-722.			✓		✓	✓	✓
Kongsakon R, Leelahanaj T, Price N, Birinyi-Strachan L, Davey P. Cost analysis of the treatment of schizophrenia in Thailand: a simulation model comparing olanzapine, risperidone, quetiapine, ziprasidone and haloperidol. *Journal of the Medical Association of Thailand* 2005; 88(9): 1267-1277.	✓		✓		✓	✓	✓
McIntyre RS, Cragin L, Sorensen S, Naci H, Baker T, Roussy JP. Comparison of the metabolic and economic consequences of long-term treatment of schizophrenia using ziprasidone, olanzapine, quetiapine and risperidone in Canada: a cost-effectiveness analysis. *Journal of Evaluation in Clinical Practice* 2010; 16 (4) : 744-755.		✓	✓		✓	✓	✓
Mortimer A, Williams P, Meddis D. Impact of side-effects of atypical antipsychotics on non-compliance, relapse and cost. *Journal of International Medical Research* 2003; 31(3): 188-196.	✓		✓		✓	✓	✓
Mould Q J, Contreras H I, Verduzco W, Mejia A J M, Garduno E J, Cost-effectiveness			✓		✓		✓

simulation analysis of schizophrenia at the Instituto Mexicano del Seguro Social: Assessment of typical and atypical antipsychotics. *Revista de Psiquiatria y Salud Mental* 2009; 2(3):108-118.							
Obradovic M, Mrhar A, Kos M. Cost-effectiveness of antipsychotics for outpatients with chronic schizophrenia. *International Journal of Clinical Practice* 2007; 61(12):1979-1988.			✓		✓	✓	✓

Table A4.2. Economic analyses ('economic burden of condition' and/or 'cost-of-illness'): format availability and use to inform development of economic commentary

Key
A: NHS EED structured abstract record
B: NHS EED citation only record
C: HEED field-coded abstract record
D: HEED citation only record
E: Article abstract
F: Article full-text
G: Used to inform development of economic commentary

Kamal 2011							
Citation	*A*	*B*	*C*	*D*	*E*	*F*	*G*
Alexandrov A V, Smurawska L T, Bartle W, Oh P. Cost considerations in the pharmacological prevention and treatment of stroke. *Pharmacoeconomics* 1997; 11(5): 408-418.			✓		✓	✓	
Bakhai A. The burden of coronary, cerebrovascular and peripheral arterial disease. *Pharmacoeconomics* 2004; 22(suppl 4): 11-18.			✓		✓	✓	
Bergman L, van der Meulan J H P, Limburg M, Habbema J D F. Cost of medical care after first-ever stroke in the Netherlands. *Stroke* 1995; 26: 1830-1836.			✓		✓	✓	
Cadilhac D A, Carter R, Thrift A G, Dewey H M. Estimating the long-term costs of ischemic and hemorrhagic stroke for Australia: new evidence derived from the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke* 2009; 40(3): 915-921.				✓	✓	✓	
Caro J J, Huybrechts K F, Duchesne I. Management patterns and costs of acute ischemic stroke : an international study. *Stroke* 2000; 31: 582-590.		✓	✓		✓	✓	
Caro J J, Migliaccio-Walle K, Ishak K J, Proskorovsky I, O'Brien J A. The time course of subsequent hospitalizations and associated costs in survivors of an ischemic stroke in Canada. *BMC Health Services Research* 2006; 6(99).		✓			✓	✓	
Christensen M C, Munro V. Ischemic stroke and intracerebral hemorrhage: the latest evidence on mortality, readmissions and hospital costs from Scotland.		✓			✓	✓	

Neuroepidemiology 2008; 30(4): 239-246.							
Christensen M C, Valiente R, Sampaio Silva G, Lee W C, Dutcher S, Guimaraes Rocha M S, Massaro A. Acute treatment costs of stroke in Brazil. *Neuroepidemiology* 2009; 32(2): 142-149.			✓		✓	✓	
Christensen M C, Previgliano I, Capparelli F J, Lerman D, Lee W C, Wainsztein N A. Acute treatment costs of intracerebral hemorrhage and ischemic stroke in Argentina. *Acta Neurologica Scandinavica* 2009; 119: 246-253.			✓		✓	✓	
Flynn R W, MacWalter R S, Doney A S. The cost of cerebral ischaemia. *Neuropharmacology* 2008; 55(3): 250-256.		✓			✓	✓	✓
Gioldasis G, Talelli P, Chroni E, Daouli J, Papapetropoulos T, Ellul J. In-hospital direct cost of acute ischemic and hemorrhagic stroke in Greece. *Acta Neurologica Scandinavica* 2008; 118: 268-274.			✓		✓	✓	
Kolominsky-Rabas P L, Heuschmann P U, Marschall D, Emmert M, Baltzer N, Neundorfer B, Schoffski O, Krobot K J. Lifetime cost of ischemic stroke in Germany: results and national projections from a population-based stroke registry - the Erlangen Stroke Project. *Stroke* 2006; 37(5): 1179-1183.		✓			✓	✓	
Naylor T N, Davis P H, Torner J C, Holmes J, Meyer J W, Jacobson M F. Lifetime cost of stroke in the United States. *Stroke* 1996; 27(9): 1459-1466.			✓		✓	✓	
Payne K A, Huybrechts K F, Caro J J, Green T J C, Klittich W S. Long term cost-of-illness in stroke: an international review. *Pharmacoeconomics* 2002; 20(12):813-825.			✓		✓	✓	✓
Porsdal V, Boysen G. Costs of health care and social services during the first year after ischemic stroke. *International Journal of Technology Assessment in Health Care* 1999; 15(3): 573-584.		✓	✓		✓	✓	
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N/A - No relevant or potentially useful economic analyses identified.							

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Appendix 5. NHS EED and HEED records of economic evaluations and economic analyses cited in economic commentaries

Kamal 2011: Economic evaluations

Inoue 2006: NHS EED record

Pharmacoeconomic analysis of cilostazol for the secondary prevention of cerebral infarction
Inoue T, Kobayashi M, Uetsuka Y, Uchiyama S

Health technology	The use of 200 mg/day cilostazol for the secondary prevention of cerebral infarction.
Type of intervention	Secondary prevention.
Hypothesis/study question	The objective of the study was to calculate the health outcomes and associated costs of treating 65-year-old patients with cilostazol after they had suffered a cerebral infarction. The comparator chosen was 81 mg/day aspirin. The authors also evaluated the use of no prophylaxis. The rationale for the study was that cilostazol may be highly effective in reducing the risk of subsequent cerebral infarction in comparison with aspirin, although it is more expensive. The perspective adopted in the economic analysis was that of a publicly funded health insurance.
Economic study type	Cost-utility analysis.
Study population	The study population comprised a hypothetical cohort of 65-year-old men with first-ever ischaemic stroke (Barthel Index, BI=100).
Setting	The study setting was not explicitly stated, but it might have been both secondary care and primary care. The economic study was carried out in Japan.
Dates to which data relate	The effectiveness data were derived from studies published between 1991 and 2004. The price year was not explicitly reported, but it appears to have been 2004.
Source of effectiveness data	The effectiveness data were derived from a review of published studies.
Modelling	A Markov model was developed to estimate the health outcomes and costs. The model comprised four stages: prophylactic treatment after first stroke; acute stage of recurrent cerebral infarction; chronic stage after recurrence of cerebral infarction; and death. The time horizon was not specified, although it would appear to relate to the patient's lifetime.
Outcomes assessed in the review	The outcomes assessed were:

	the rate of cerebral infarction recurrence without prophylaxis, the relative risk of cerebral infarction recurrence, the rate of intra- and extra-cranial bleeding, mortality due to cerebral infarction, all other causes of mortality, and the relative risk of mortality after recurrence by different levels of severity, as determined by the BI.
Study designs and other criteria for inclusion in the review	Not reported.
Sources searched to identify primary studies	Not reported.
Criteria used to ensure the validity of primary studies	Not reported.
Methods used to judge relevance and validity, and for extracting data	Not reported.
Number of primary studies included	Approximately six studies were included in the review of the literature. The authors used a meta-analysis and a double-blind randomised controlled trial to derive the recurrence rates for stroke and adverse events, and the results from one trial to derive the rates of haemorrhagic adverse events. The natural death rate at each stage was derived from Japanese life tables, while mortality rates after cerebral infarction recurrence were derived from data from a Japanese prefecture.
Methods of combining primary studies	Not relevant.
Investigation of differences between primary studies	Not relevant.
Results of the review	The rate of cerebral infarction recurrence without prophylaxis was 0.0578. The relative risk of cerebral infarction recurrence was 0.77 with aspirin and 0.583 with cilostazol. The rate of intracranial bleeding was 0.0041 with aspirin and 0 with cilostazol. The rate of extracranial bleeding was 0.0034 with aspirin and 0 with cilostazol. The relative risk of mortality after recurrence ranged from 1.2 (BI=81) to 13 (BI=0).
Measure of benefits used in the economic analysis	The measure of benefits used was the quality-adjusted life-years (QALYs). As no utility values have been estimated in Japan, the authors used the representative BI value (adding the minimum and maximum values for each BI category and dividing by 2) as the respective utility value. The utility values the authors used were 1 (BI=100), 0.9 (BI of 81 - 99), 0.705 (BI of 61 - 80), 0.49 (BI of 38 - 60), 0.19 (BI of 1 - 37) and 0.1 (BI=0).
Direct costs	The direct costs included in the analysis were those of the health care system.

	Such costs were for drugs, treatment for gastrointestinal bleeding, treatment for recurrence of cerebral infarction, and long-term care following recurrence. The costs of the drugs were derived from official reimbursement price lists. The costs of treating intracranial haemorrhage due to recurrence were derived from a published study. The costs of long-term care were derived from the Japanese Ministry of Health, Labour, and Welfare. Since the costs were incurred over the lifetime of the patient, the costs were appropriately discounted at an annual rate of 3%. The study reported the average costs per patient. The price year was not explicitly reported, but it appears to have been 2004.
Indirect Costs	The indirect costs were not included.
Currency	Japanese yen (JPY).
Statistical analysis of costs	The costs were treated as point estimates (i.e. the data were deterministic).
Sensitivity analysis	One-way sensitivity analyses were performed on all of the main parameters of the analysis, except utility values. The parameters were varied within a 50% decrease or increase from the base values. For utility values, the effect of varying the estimates was determined using Monte Carlo simulation, which randomly extracted the utility value for each BI category from a uniform distribution and had the range of each BI category as the upper and lower limit.
Estimated benefits used in the economic analysis	The QALYs gained were 11.15 with aspirin, 10.8 with no prophylaxis, and 11.79 with cilostazol.
Cost results	The average cost per patient was JPY 2,891,063 with aspirin, JPY 3,343,401 with no prophylaxis, and JPY 4,038,081 with cilostazol.
Synthesis of costs and benefits	The costs and benefits were combined using an incremental cost-utility ratio (i.e. the additional cost per QALY gained). Both the cilostazol and no prophylaxis strategies were compared with aspirin. No prophylaxis was found to be dominated by the aspirin strategy (i.e. the aspirin strategy was both cheaper and more effective than no prophylaxis). Compared with aspirin, the additional cost per QALY gained was JPY 1,792,216 using the cilostazol strategy. The results of the one-way sensitivity analyses showed that varying the relative risk for recurrence of cerebral infarction in the cilostazol and aspirin groups had the greatest effect on cost-effectiveness. The monthly cost of treatment in the cilostazol group and the recurrence rate of cerebral infarction in the untreated groups were the next most influential parameters. The results of the Monte Carlo simulation on utility values showed that the minimum incremental cost-utility ratio was JPY 1.78 million and the maximum was JPY 2.05 million for cilostazol compared with aspirin.
Authors' conclusions	The use of cilostazol to prevent cerebral infarction recurrence would appear to be cost-effective. The authors reported that an incremental cost-utility ratio of JPY 1.79 million was not unreasonable if one took into account the willingness to pay for an additional quality-adjusted life-year (QALY) from agencies such as the National Institute for Clinical Excellence in the UK, which has an implicit threshold of approximately 30,000 (JPY 5.6 million).
CRD COMMENTARY - Selection of comparators	An explicit justification was given for using aspirin as the comparator. It represented an effective strategy in preventing the recurrence of cerebral

	infarction. You should decide whether the use of aspirin for the secondary prevention of cerebral infarction is current practice in your own setting.
Validity of estimate of measure of effectiveness	The authors did not report that a systematic review of the literature had been undertaken to identify relevant research and minimise biases. However, the authors appear to have made use of a meta-analysis and randomised controlled trial to derive most of the parameters for their model. The authors also appear not to have used many assumptions in their model. As reported, there was an imbalance in the quantity of information used to populate the model parameters relating to different treatments, since only one trial assessed cilostazol for the prevention of cerebral infarction recurrences. In addition, the influence of bleeding might have been underestimated in the study since some types of bleeding were not considered.
Validity of estimate of measure of benefit	The estimation of benefits was modelled. The authors reported that there were no utility measures for cerebral infarction in Japan, thus they converted the BI scores to utility values. Although the authors described the method used, they did not refer the reader to any literature and it was therefore unclear whether the method they used is common practice or valid. However, the authors appropriately varied the utility estimates in their sensitivity analysis.
Validity of estimate of costs	All the categories of cost relevant to the health care perspective adopted were included in the analysis. No major relevant costs appear to have been omitted from the analysis. The costs and the quantities were not reported separately, which will limit reflation exercises to other settings. The costs were derived from published sources. All costs were appropriately varied in a one-way sensitivity analysis using wide ranges (+/-50%). As the costs were incurred over the lifetime of the patient, all future costs were appropriately discounted. The price year was not explicitly reported, which will hamper future inflation exercises.
Other issues	The authors made appropriate comparisons of their findings with those from other studies that had also found secondary prophylaxis for cerebral infarction to be cost-effective. Although it was not explicitly stated in the paper, the issue of generalisability to other settings was partly addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The main limitation reported by the authors was that they found no estimates of utility values applicable in Japan.
Implications of the study	The authors recommended that the results of their analysis be re-examined within a certain period of time, as changes in the drug prices and in medical treatment fees may vary in the future.
Source of funding	Supported by Otsuka Pharamceutical Co. Ltd, Otsuka, Japan.
Bibliographic detail	Inoue T, Kobayashi M, Uetsuka Y, Uchiyama S. Pharmacoeconomic analysis of cilostazol for the secondary prevention of cerebral infarction. Circulation Journal 2006; 70(4): 453-458
Link to Pubmed record	16565564
Other publications of related interest	Sarasin FP, Gaspoz JM, Bounameuaux H. Cost-effectiveness of new antiplatelet regimens used as secondary prevention of stroke or transient ischemic attack. Arch Intern Med 2000;160:2773-8.

	Gaspoz JM, Coxson PG, Goldman PA, et al. Cost-effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. N Engl J Med 2002;346:1800-6. Holloway RG, Benesch CG, Rahilly CR, et al. A systematic review of cost-effectiveness research of stroke evaluation and treatment. Stroke 1999;30:1340-9.
Subject index terms status	Subject indexing assigned by CRD
Subject index terms	Aged; Aspirin /economics /therapeutic use; Case-Control Studies; Cerebral Infarction /drug therapy /economics /prevention & control; Cost-Benefit Analysis; Health Care Costs; Humans; Male; Markov Chains; Models, Econometric; Models, Statistical; Platelet Aggregation Inhibitors /economics /therapeutic use; Quality-Adjusted Life Years; Tetrazoles /economics /therapeutic use; Time Factors
Accession number	22006000765
Database entry date	31 August 2006
Record status	This is a critical structured abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Inoue 2006: HEED record

Article Reference No	015719
Author	Inoue T, Kobayashi M, Uetsuka Y, Uchiyama S
Article Title	Pharmacoeconomic analysis of cilostazol for the secondary prevention of cerebral infarction
Journal Name	Circulation Journal
Journal Date	2006
Journal Reference	70:453-458
Publication Status	Published in a journal of unknown status
Availability Details	Correspondence: Tadeo Inoue, PhD, Department of Pharmacy, St LukeÆs International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan. E-mail: tadaoino@luke.org.jp
Cost Base Year	2004
Source Of Article	O
Countries Of Authors	Japan
Countries Applicable	Japan
Type Of Article	Applied study
Type Of Econ Eval	Cost effectiveness analysis;Cost utility analysis
Technology Assessed	Pharmaceutical
ATC Codes	B01A
ICD-9 Codes	434
Drug Names	ASPIRIN; CILOSTAZOL
Prob. of Main Clinical Events	Observational data;Other literature review
Quantities of Resources Used	Judgement;Modelling
Prices or Costs of Resources	National Publication
Outcomes	Observational data;Other literature review;Modelling
Values Of Outcomes	Previously Published Values
Outcome Measure	Quality-adjusted life years (QALYs)
Costs Included	Hospital costs;Direct provider/purchaser costs
Costs Discounted	3%
Benefits Discounted	3%
Sensitivity Tested	Sensitivity tested
Quantitatively Reported	Quantitatively reported
Study Question	A Markov model was developed to evaluate the costs and effects of cilostazol for the secondary prevention of cerebral infarction, using the health service perspective. The main outcome measure was quality-adjusted life year (QALY) gained. Medical costs and long-term care costs were estimated. Costs and effects were discounted at

	a rate of 3%. Sensitivity analysis was performed to test the robustness of the cost-effectiveness results.
Key Results	Study findings suggest that cilostazol may be cost-effective in preventing recurrence of cerebral infarction. Lifetime cost for aspirin was Yen 2.89; for the group that received no prophylactic treatment lifetime cost was Yen 3.34 million, and for the group that received cilostazol prophylaxis lifetime costs was Yen 4.04 million. Cilostazol was associated with the highest quality-adjusted life years (QALYs), 10.80 for the untreated group, 11.15 QALYs for the aspirin group and 11.79 QALYs for the cilostazol group). The aspirin strategy was the dominant strategy when compared to the untreated group and the cilostazol group. When compared to the aspirin group, the incremental cost-effectiveness ratio was Yen1.79 million for the cilostazol group.
Patient Group	A cohort of 65-year old men with first-ever ischemic stroke were considered for the present analysis.
Sponsor	Pharmaceutical industry
Keywords	Applied Study;Cerebrovascular Disease; Stroke;Pharmacoeconomics;QALYs;Quality Adjusted Life Years;Models;Direct Costs;Cost Utility Analysis;Cost Effectiveness Analysis (CEA)

Brito 2011: Economic evaluations

Latour-Perez 2009: NHS EED record

Cost effectiveness of fondaparinux in non-ST-elevation acute coronary syndrome
Latour-Perez J, De-Miguel-Balsa E

Record status	This is an economic evaluation that meets the criteria for inclusion on NHS EED. If you would like us to consider prioritising the writing of a critical abstract for this economic evaluation please e-mail: CRD-NHSEED@york.ac.uk quoting the Accession Number of this record. Please note that priority is given to fast track requests from the UK National Health Service.
Bibliographic detail	Latour-Perez J, De-Miguel-Balsa E. Cost effectiveness of fondaparinux in non-ST-elevation acute coronary syndrome. Pharmacoeconomics 2009; 27(7): 585-595
Link to Pubmed record	19663529
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Acute Coronary Syndrome /drug therapy /economics; Anticoagulants /economics /therapeutic use; Cost-Benefit Analysis; Data Interpretation, Statistical; Decision Support Techniques; Electrocardiography; Humans; Markov Chains; Polysaccharides /economics /therapeutic use
Accession number	22009103662
Database entry date	2 June 2010

Latour-Perez 2009: HEED record

Article Reference No	075288
Author	Latour-Perez J, de Miguel-Balsa E
Article Title	Cost effectiveness of fondaparinux in non-ST-elevation acute coronary syndrome
Journal Name	PharmacoEconomics
Journal Date	2009
Journal Reference	27(7):585-595
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence: Dr Jaime Latour-Perez, Servicio de Medicina Intensiva, Hospital General Universitario de Elche, Cami Vell de lÆAlmassera 11, 03203 Elche, Spain. E-mail: jlatour@coma.es
Cost Base Year	2006
Source Of Article	O
Countries Of Authors	Spain
Countries Applicable	Spain
Type Of Article	Applied study
Type Of Econ Eval	Cost utility analysis
Technology Assessed	Pharmaceutical
ATC Codes	B01A
ICD-9 Codes	411
Drug Names	FONDAPARINUX; ENOXAPARIN
Prob. of Main Clinical Events	Observational data;Other literature review
Quantities of Resources Used	Judgement;Modelling
Prices or Costs of Resources	'Ad Hoc' Estimation
Outcomes	Observational data;Other literature review;Modelling
Outcome Measure	Risk of major bleeding, adverse cardiac events, length of life, quality adjusted life years (QALYs)
Source Of Data	Incorporated from another study
Costs Included	Hospital costs;Direct provider/purchaser costs
Costs Discounted	3%
Benefits Discounted	3%
Sensitivity Tested	Sensitivity tested
Quantitatively Reported	Quantitatively reported
Abstract	Background: Fondaparinux has been shown to reduce the risk of major bleeding and 30-day mortality compared with enoxaparin, in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS). However, its cost effectiveness is not well known. Objective:

	To evaluate the effectiveness and economic attractiveness of fondaparinux relative to enoxaparin in patients with NSTE-ACS treated with triple antiplatelet therapy and early (non-urgent) invasive strategy. Methods: The decision model compares two alternative strategies: subcutaneous (SC) enoxaparin (1mg/kg 12 hourly) versus SC fondaparinux (2.5mg/day) in NSTE-ACS patients pre-treated with triple antiplatelet therapy and early revascularization. Cost-effectiveness and cost-utility analyses were performed from a healthcare perspective, based on a Markov model with a time horizon of the patient lifespan. Univariate sensitivity analysis and probabilistic (Monte Carlo) microsimulation analysis were performed. Results: In the base-case analysis (65 years, Thrombolysis In Myocardial Infarction [TIMI] score 4), the use of fondaparinux was associated with a significant reduction in major bleeding, a slight reduction in adverse cardiac events, and minor improvements in survival and QALYs, together with a small reduction in costs. The dominance of fondaparinux over enoxaparin remained unchanged in the univariate sensitivity analyses. According to Monte Carlo simulation, fondaparinux was cost saving in 99.9% of cases. Conclusion: Compared with enoxaparin, the use of fondaparinux in patients with NSTE-ACS managed with an early invasive strategy appears to be cost effective, even in patients with a low risk of bleeding. Reproduced by kind permission of Adis International Limited
Study Question	The objective of this study was to evaluate the effectiveness and economic attractiveness of fondaparinux relative to enoxaparin in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) treated with triple antiplatelet therapy and early (non-urgent) invasive strategy. A decision model was used to compare two alternative strategies: subcutaneous (SC) enoxaparin (1mg/kg 12 hourly) versus SC fondaparinux (2.5mg/day) in NSTE-ACS patients pre-treated with triple antiplatelet therapy and early revascularization. Cost-effectiveness and cost-utility analyses were performed from a healthcare perspective, based on a Markov model with a time horizon of the patient lifespan. Univariate sensitivity analysis and probabilistic (Monte Carlo) microsimulation analysis were performed
Key Results	Under the reference case (65 years of age and a Thrombolysis In Myocardial Infarction [TIMI] score of 4), the use of fondaparinux was associated with a lower expected cost per patient, a lower rate of bleeding, a lower rate of major cardiac events, a higher expected survival and more quality adjusted life years (QALYs) than enoxaparin. The use of fondaparinux under the base-case scenario was cost saving. The dominance of fondaparinux over enoxaparin persisted in the one-way cost-effectiveness sensitivity analyses for all the variables considered, except in those hypothetical scenarios of relative risk of bleeding with fondaparinux = or > 1. According to the Monte Carlo simulation, the use of fondaparinux was cost

	saving in 99.9% of the cases and cost effective in the remaining 0.1%. The incremental net health benefit (NHB varied slightly with the threshold willingness to pay (from 0.025 to 0.021 for a threshold of Euros 10 000 and Euros 70 000 per QALY, respectively). The authorsÆ concluded that compared with enoxaparin, the use of fondaparinux in patients with NSTE-ACS managed with an early invasive strategy appears to be cost effective, even in patients with a low risk of bleeding.
Patient Group	Patients with non-ST-elevation acute coronary syndrome (NSTE-ACS). In the base-case analysis the patient was 65 years of age and had a Thrombolysis In Myocardial Infarction (TIMI) score of 4
Keywords	Cost Utility Analysis;QALYs;Quality Adjusted Life Years;Modelling;Pharmaceutical;Cost Effectiveness - General Discussion CBA/CEA

Maxwell 2009: NHS EED record

Cost-effectiveness analysis of anticoagulation strategies in non-ST-elevation acute coronary syndromes

Maxwell CB, Holdford DA, Crouch MA, Patel DA

CRD summary	The objective was to compare the cost-effectiveness of four anticoagulation regimens that were recommended for moderate-to-high-risk patients with non-ST-elevation acute coronary syndrome. Bivalirudin was the least costly anticoagulation therapy for early invasive treatment, and fondaparinux was preferred for patients undergoing conservative treatment. The methods were satisfactory and they and the results were well reported. The authors' conclusions appear to be appropriate.
Type of economic evaluation	Cost-effectiveness analysis
Study objective	The objective was to compare the cost-effectiveness of four anticoagulation regimens that were recommended for moderate-to-high-risk patients with non-ST-elevation acute coronary syndrome.
Interventions	The four antithrombotic treatments were unfractionated heparin with a glycoprotein inhibitor, enoxaparin with a glycoprotein inhibitor, bivalirudin alone, and fondaparinux with a glycoprotein inhibitor. The dosages were reported.
Location/setting	USA/secondary care.
Methods	Analytical approach: A decision tree was used to synthesise the data from published clinical trials for the four treatment regimens. For each treatment arm of the decision tree, a patient followed a treatment path either with or without complications. The authors stated that the perspective was that of a health care provider. Effectiveness data: The clinical evidence was identified from recent available anticoagulation studies that compared the four strategies. The procedural techniques, complication rates, and treatment regimens were closely based on those of the Superior Yield of the New strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa inhibitors (SYNERGY), the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5), and ACUITY trials, which were the main motivation and data sources for this study. The outcomes and probabilities associated with each treatment strategy were derived from point estimates reported in these three trials. A literature review was conducted to obtain the data on consistent anticoagulation in patients. Monetary benefit and utility valuations: Not relevant. Measure of benefit: The measure of benefit was patients treated without complications, as this was the only clinically significant difference between the treatments. Cost data: The cost categories were the treatment, drug acquisition, and complications of the interventions. The drug acquisition costs were from the wholesaler-purchasing database of the Virginia Commonwealth University Medical Center. The major complication costs were based on diagnosis-related group data. Physician fees were estimated by assigning a Current Procedural Terminology (CPT) code to all complications. The minor complication (bleeding) costs were from hospital blood bank reports. The resource use data

	were from published clinical trials that sampled moderate-to-high-risk patient populations. All costs were reported in US dollars ($). Analysis of uncertainty: One-way, two-way, and probabilistic sensitivity analyses were performed. The results were presented in a tornado diagram and a cost-effectiveness acceptability curve. Scattergrams were also generated from 100,000 Monte Carlo simulations.
Results	Bivalirudin was the least costly treatment and it dominated enoxaparin and unfractionated heparin, as bivalirudin was less costly and more effective. The number of complications associated with fondaparinux and the glycoprotein inhibitor eptifibatide were slightly lower than those associated with bivalirudin alone. The sensitivity analyses revealed that unfractionated heparin was never cost-effective compared with fondaparinux or bivalirudin, and that bivalirudin and fondaparinux were superior in most of the analyses. The results of the scattergrams were inconclusive, as the simulated points were spread evenly around the acceptability plane.
Authors' conclusions	Bivalirudin was the least costly anticoagulation therapy for early invasive treatment, and fondaparinux was preferred for patients undergoing conservative treatment.
CRD commentary	Interventions: The interventions were well described and appear to have been appropriate comparators. Effectiveness/benefits: The effectiveness data were mainly from contemporary studies that were highly relevant and appear to have been appropriate. The authors also conducted a literature review, which implies that the three clinical trials were not identified in this way and this makes it difficult to ascertain whether all relevant evidence was included. QALYs would have been a more appropriate benefit measure, as they would have made cross-disease comparisons possible and measured the impact of the disease on both quality of life and survival. The reasons for using a different benefit measure were stated and appear to have been justified. The authors did not report discounting of the benefits nor the time line of the study, and this might lead to inconsistencies in the data and could increase the uncertainty in the results. Costs: The costs were relevant to the perspective. The cost estimates appear to have been appropriately derived from the study setting, but wholesale costs and Medicare reimbursement data were used and these might not represent the costs for all patients in the population. The authors did not report any discounting of the costs and they did not state the price year. Analysis and results: The model was well described and all the costs and benefits of the base case were reported. The synthesis of the data appears to have been appropriate and a comprehensive analysis of uncertainty was undertaken. There were several limitations to the study, which the authors identified and discussed. Most of the data were from clinical trials that might not have reflected the true complication rates. Concluding remarks: The methods were satisfactory and they and the results were well reported. The authors' conclusions appear to be appropriate.
Source of funding	Not stated.
Bibliographic details	Maxwell CB, Holdford DA, Crouch MA, Patel DA. Cost-effectiveness analysis

	of anticoagulation strategies in non-ST-elevation acute coronary syndromes. Annals of Pharmacotherapy 2009; 43(4): 586-595
Link to Pubmed record	19336655
URL for original research	http://www.theannals.com/cgi/content/abstract/43/4/586
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Acute Coronary Syndrome /drug therapy /economics; Anticoagulants /economics /therapeutic use; Cost-Benefit Analysis; Humans; Randomized Controlled Trials as Topic /economics
Accession number	22009101973
Database entry date	13 October 2010
Record status	This is a critical structured abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Maxwell 2009: HEED record

Article Reference No	075257
Author	Maxwell C B, Holdford D A, Crouch M A, Patel D A
Article Title	Cost-effectiveness analysis of anticoagulation strategies in non-ST-elevation acute coronary syndromes
Journal Name	The Annals of Pharmacotherapy
Journal Date	2009
Journal Reference	43(5):586-595
Publication Status	Published in a peer reviewed journal
Availability Details	Reprints: Dr Michael Crouch, 709 Mall Boulevard, Savannah, GA 31406, USA. E-mail: mcrouch@southuniversity.edu
First Year Clinical Data	1966
Last Year Clinical Data	2008
Source Of Article	O
Countries Of Authors	USA
Countries Applicable	USA
Type Of Article	Applied study
Type Of Econ Eval	Cost effectiveness analysis
Technology Assessed	Pharmaceutical
ATC Codes	B01A
ICD-9 Codes	410; 429
Drug Names	EPTIFIBATIDE; ENOXAPARIN; BIVALIRUDIN; FONDAPARINUX
Prob. of Main Clinical Events	Randomised clinical trial
Quantities of Resources Used	Randomised clinical trial
Prices or Costs of Resources	'Ad Hoc' Estimation
Outcomes	Randomised clinical trial
Outcome Measure	Each additional patient treated without complication
Costs Included	Hospital costs;Direct provider/purchaser costs
Sensitivity Tested	Sensitivity tested
Quantitatively Reported	Quantitatively reported
Study Question	The objective of this decision analysis study was to perform a cost-effectiveness analysis comparing 4 anticoagulant regimens in non-ST-elevation acute coronary syndrome (NSTE-ACS). Data sources were taken from the SYNERGY, OASIS-5, and ACUITY trials, including 2 subgroup analyses. The study was conducted from a

	healthcare provider perspective
Key Results	Overall bivalirudin alone was the least costly regimen (US$1131 per average course) and it dominated (i.e., was more effective and cost less) both enoxaparin plus eptifibatide ($1609) and unfractionated heparin (UFH) plus eptifibatide (US$1739) in cost-effectiveness. The number of complications seen with fondaparinux and eptifibatide was slightly lower than with bivalirudin alone, but the average cost of treatment was slightly higher (US$1184). When compared with bivalirudin, the incremental cost of fondaparinux for each additional patient treated without complications was US$2569. Sensitivity analyses showed the model's results to be sensitive to drug acquisition cost and complication probabilities. Probabilistic sensitivity analyses favored neither bivalirudin nor fondaparinux; however, when 2 or more vials of bivalirudin were necessary, bivalirudin was no longer a cost-effective alternative. The authorsÆ concluded that bivalirudin is the least costly agent in moderate- to high-risk non-ST-elevation acute coronary syndrome (NSTE-ACS) patients managed with an early invasive approach, if its use is consistent with the ACUITY trial. Fondaparinux is the preferred agent in patients undergoing a conservative treatment strategy.
Patient Group	Patients with non-ST-elevation acute coronary syndrome (NSTE-ACS)
Keywords	Cost Effectiveness Analysis (CEA);Pharmaceutical;Myocardial Infarction;Decision Analysis

Sculpher 2009: NHS EED record

Fondaparinux versus Enoxaparin in non-ST-elevation acute coronary syndromes: short-term cost and long-term cost-effectiveness using data from the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (OASIS-5) trial

Sculpher M J, Lozano-Ortega G, Sambrook J, Palmer S, Ormanidhi O, Bakhai A, Flather M, Steg P G, Mehta S R, Weintraub W

Record status	This is an economic evaluation that meets the criteria for inclusion on NHS EED. If you would like us to consider prioritising the writing of a critical abstract for this economic evaluation please e-mail: CRD-NHSEED@york.ac.uk quoting the Accession Number of this record. Please note that priority is given to fast track requests from the UK National Health Service.
Bibliographic detail	Sculpher M J, Lozano-Ortega G, Sambrook J, Palmer S, Ormanidhi O, Bakhai A, Flather M, Steg P G, Mehta S R, Weintraub W. Fondaparinux versus Enoxaparin in non-ST-elevation acute coronary syndromes: short-term cost and long-term cost-effectiveness using data from the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (OASIS-5) trial. American Heart Journal 2009; 157(5): 845-852
Link to Pubmed record	19376310
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Acute Coronary Syndrome /drug therapy /economics; Anticoagulants /economics /therapeutic use; Cost-Benefit Analysis /methods; Electrocardiography; Enoxaparin /economics /therapeutic use; Factor X; Follow-Up Studies; Guideline Adherence; Health Care Costs /trends; Humans; Polysaccharides /economics /therapeutic use; Practice Guidelines as Topic; Time Factors; United States
Accession number	22009101604
Database entry date	9 September 2009

Sculpher 2009: HEED record

Article Reference No	059766
Author	Sculpher M J, Lozano-Ortega G, Sambrook J, Palmer S, Ormanidhi O, Bakhai A, Flather M, Steg G, Mehta S R, Weintraub W.
Article Title	Fondaparinux versus enoxaparin in non-ST-elevation acute coronary syndromes: short-term cost and long-term cost-effectiveness using data from the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators (OASIS-5) trial
Journal Name	Americal Heart Journal
Journal Date	2009
Journal Reference	157:845-852
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence to: Mark J. Sculpher, PhD, Centre for Health Economics, University of York, Heslington, York, YO10 5DD, United Kingdom. E-mail: mjs23@york.ac.uk.
First Year Clinical Data	2003
Last Year Clinical Data	2005
First Year Cost Data	2003
Last Year Cost Data	2005
Cost Base Year	2006
Source Of Article	O
Countries Of Authors	UK, France, Canada, USA
Countries Applicable	USA
Type Of Article	Applied study
Type Of Econ Eval	Cost effectiveness analysis;Cost utility analysis
Technology Assessed	Pharmaceutical
ATC Codes	B01A
ICD-9 Codes	411; 433; 434; 435; 436; 437; 438
Drug Names	FONDAPARINUX; ENOXAPARIN
Prob. of Main Clinical Events	Randomised clinical trial;Judgement;Modelling
Quantities of Resources Used	Randomised clinical trial;Modelling
Prices or Costs of Resources	'Ad Hoc' Estimation;Local Standard Prices
Outcomes	Randomised clinical trial;Modelling
Values Of Outcomes	Previously Published Values
Outcome Measure	Major bleeding rate, death, myocardial infarction, stroke, Quality-adjusted life years (QALY)

Qual Of Life Index	Generic;Utility assessment;EQ-5D
Source Of Data	Incorporated from another study
Costs Included	Hospital costs;Direct provider/purchaser costs
Costs Discounted	3%
Benefits Discounted	3%
Sensitivity Tested	Sensitivity tested
Quantitatively Reported	Quantitatively reported
Study Question	Based on a randomized control trial (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators [OASIS-5]) the aim of the study was to compare the short-term costs and long-term cost-effectiveness of 2 antithrombotics, fondaparinux (2.5 mg daily) and enoxaparin (1 mg per kg twice daily), for nonûST-elevation acute coronary syndrome. Treatment was administered for a mean of 5 days. The rationale of the study was that in OASIS-5 trial, fondaparinux patients were found to have about half the rate of major bleeding 9 days after randomization and at least as good clinical outcomes (death, myocardial infarction, major bleeding and stroke) after 6 months of follow-up. To undertake the economic evaluation, health care resource use and clinical efficacy data from the trial were incorporated into a cost-effectiveness model as applied to both for the time horizon of the trial (6 months) and over the longer term (life time). A societal perspective was adopted and the setting of the study was secondary care in the United States.
Key Results	The effectiveness results showed that for each type of event over the 180-day follow-up period, fondaparinux is protective compared with enoxaparin, although this is not significant with nonfatal MI. For death, nonfatal MI and nonfatal stroke, increasing age, being male, a history of heart failure, and diabetes increase the event risk. ST depression and high creatinine at baseline increase mortality risk. Increased serum creatinine was the only predictive covariate for bleeds. The 180-day cost analysis indicated that fondaparinux would generate a cost saving of US$547 per patient (95% CI US$207-US$924). Sensitivity analysis suggested that savings could vary between US$494 and US$733. As well as mean (expected) cost-effectiveness, the probability of each therapy being the least costly and the more cost-effective assuming a cost-effectiveness threshold of US$50,000 per QALY gained was presented using probabilistic sensitivity analysis. Fondaparinux was predicted to generate a $188 saving and 0.04 additional QALYs in the ôaverageö OASIS-5 patient. However, when 180-day cost and clinical results were extrapolated to long-term cost-effectiveness, fondaparinux was dominant (less costly and more effective in terms of quality-adjusted life-years) under most scenarios. The authors concluded that fondaparinux is a more cost-effective antithrombotic agent than enoxaparin in nonûST-elevation acute coronary syndrome. This is true across the range of event risks seen in the OASIS-5 trial, which

	informed the present modelling study.
Patient Group	The patient group comprised of 20,078 male and female patients with nonûST-elevation acute coronary syndrome. Patients participated in the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators [OASIS-5] trial. The economic analysis was based on a sub-sample of 759 trial patients.
Sponsor	Pharmaceutical industry
Keywords	Coronary Heart Disease;Coronary - Artery Disease;Acute Care;Cost Effectiveness;Cost Effectiveness Analysis (CEA);Cost Utility;Cost Utility Analysis;QALYs;Quality Adjusted Life Years;Thrombolytic Agents - Medications;Thrombosis

Dasari 2011: Economic evaluations

Dupree 2002: NHS EED record

Advantages of laparoscopic resection for ileocecal Crohn's disease
Duepree H J, Senagore A J, Delaney C P, Brady K M, Fazio V W

Health technology	The use of laparoscopic surgery (LAP) for surgical resection was studied in patients with ileocecal Crohn's disease. The comparator treatment was the same surgery carried out by laparotomy (OPEN).
Type of intervention	Treatment.
Hypothesis/study question	The aim of the study was to assess the cost-effectiveness of LAP for patients with ileocecal Crohn's disease. The comparator was the same surgery carried out by OPEN, which is the alternative surgical treatment. Although the perspective adopted in the economic analysis was not clearly stated, it appears to have been that of the hospital.
Economic study type	Cost-effectiveness analysis.
Study population	The population comprised patients undergoing elective initial resection for ileocecal Crohn's disease. Patients had to have no sign of enterocutaneous fistula or prior bowel resections.
Setting	The setting was secondary care. The economic study was carried out in Ohio, USA.
Dates to which data relate	The effectiveness evidence and resource evidence related to 1999 to 2000. The price year was 2000.
Source of effectiveness data	The effectiveness data were derived from a single study.
Link between effectiveness and cost data	The costing was carried out on the same patient sample as that used in the effectiveness analysis. It appears that the costing has been carried out retrospectively.
Study sample	No power calculations were reported. There was no sample selection, as all patients meeting the inclusion criteria were included. Forty-five patients were included in the study, of which 21 were in the LAP group and 24 in the OPEN group.
Study design	This was a single-centred, non-randomised controlled study in which the operating surgeon decided what type of surgery the patient should undergo. The patients were followed up until they left hospital.
Analysis of effectiveness	The analysis was conducted on an intention to treat basis. The health outcomes used to evaluate the two types of surgery were: the rate of conversion, the operating time,

	the intraoperative blood loss, the postoperative recovery times, the intraoperative and postoperative complication rates, and the time taken to return to work. The two patient groups were found not to be comparable in certain respects. The median age in the OPEN group was slightly older (39 years, range: 19 - 63) than in the LAP group (31 years, range: 19 - 54), ($p<0.05$). There was a higher ratio of females to males in the OPEN group (15:9) than in the LAP group (9:12), ($p<0.05$). The body mass index was higher in the OPEN group (26, interquartile range, IQR: 23 - 30) than in the LAP group (21, IQR: 20 - 25), ($p<0.05$).
Effectiveness results	In the LAP group, conversion to formal laparotomy was necessary in one patient (conversion rate 4.8%). The operating time in the LAP group was significantly shorter (median 75 minutes, IQR: 60 - 90) than in the OPEN group (median 98 minutes, IQR: 70 - 130), ($p<0.05$). The intraoperative blood loss was statistically significantly less in the LAP group (50 mL, IQR: 25 - 100) than in the OPEN group (100 mL, IQR: 50 - 265), ($p<0.05$). Postoperative recovery was significantly faster in the LAP group. For example, a nasogastric tube was used for 0 versus 1 day, ($p<0.05$) and there was earlier resumption of full liquids (0 versus 2 days; $p<0.05$). Patients in the LAP group also experienced earlier passage of flatus (2 versus 3 days; $p<0.05$) and an earlier time to first bowel movement (2 versus 4 days; $p<0.05$). There were no intraoperative complications in either group. The overall postoperative complication rate was not significantly different, 14.3% of LAP patients and 16.7% of OPEN patients. The time before returning to work was shorter in the LAP group (4 weeks, IQR: 3 - 6) than in the OPEN group (6 weeks, IQR: 4 - 8), ($p<0.05$).
Clinical conclusions	The authors concluded that, in their hospital with surgeons experienced in LAP, patients did not suffer any harm undergoing LAP for ileocecal Crohn's disease and were able to resume normal activities earlier than if they had undergone surgery with OPEN.
Measure of benefits used in the economic analysis	No summary measure of benefits was produced. The study was, in effect, a cost-consequences analysis.
Direct costs	It would appear that the perspective adopted was that of the hospital. No discounting was carried out since the costs were incurred during less than a year. The costs included were those for laboratory services, pharmacy, radiology, anaesthesia, operating room and hospitalisation, and disposable operative equipment. The patient costs were not broken down into quantities and costs. Hospital costs per patient were calculated using actual data provided by the hospital. The price year was 2000.
Indirect Costs	No indirect costs were included.

Currency	US dollars ($).
Statistical analysis of costs	No statistical analysis was carried out.
Sensitivity analysis	No sensitivity analysis was carried out.
Estimated benefits used in the economic analysis	See the 'Effectiveness Results' section.
Cost results	The cost per patient was $2,547 in the LAP group and $2,985 in the OPEN group, ($p<0.05$). The costs until discharge were included. The costs of adverse effects were dealt with in the costing. It was unclear whether the 2 patients in the LAP group who were readmitted had the costs of their readmission included.
Synthesis of costs and benefits	The costs and benefits were not combined as the study was, in effect, a cost-consequences analysis.
Authors' conclusions	Laparoscopic surgery (LAP) was cheaper than laparotomy (OPEN) for patients with ileocecal Crohn's disease. It also brought with it the advantages of quicker recovery time and an earlier return to work.
CRD COMMENTARY - Selection of comparators	The choice of the comparator (conventional surgery via OPEN) was justified by it being the surgical alternative to LAP in many settings. You should decide if it represents current practice in your own setting.
Validity of estimate of measure of effectiveness	The effectiveness data were derived from a single study. The analysis was based on a non-randomised trial with concurrent controls. A randomised controlled trial (RCT) would have provided a more robust estimate of effectiveness, as well-conducted RCTs are considered the 'gold' standard when comparing different health interventions. The fact that the patients were non-randomly allocated to the type of surgery means that the conclusions cannot be extrapolated to all patients needing resection. The study sample was representative of the study population since all patients meeting the inclusion criteria were included in the study. The patients groups were shown not to be comparable at analysis and adjustments for confounding factors were not performed. This is another drawback to the study. The analysis of effectiveness was handled credibly in that the authors acknowledged the disadvantages of a non-randomised trial. They also realised that the study was short term only, and that a full evaluation of the two types of surgery would require a longer follow-up. There were no other sources for the effectiveness data.
Validity of estimate of measure of benefit	The authors did not derive a summary measure of health benefit. The health benefits were therefore those associated with the effectiveness outcomes.
Validity of estimate of costs	Given the cost perspective adopted, which appears to have been that of the hospital, it was unclear whether all the relevant costs were included in the study. For example, it was unclear whether staff physician costs and costs of hospital readmissions were included. If the costs of hospital readmissions were not, this would have biased the results towards underestimating the cost of LAP. The authors reported that some costs were not included, these being described as

	"indirect fixed and variable indirect costs", but these were not defined. It was not clear whether these cost omissions could have biased the authors' results. The health care costs were not calculated after hospital discharge, and it was unclear whether this would have biased the cost results in a particular direction. The costs were not reported separately from the quantities. There was also very little cost information provided, which would make it difficult for decision-makers in other settings to assess the cost results. The resource use quantities were taken from a single study alone, while the prices were taken from the authors' setting only. No analyses were carried out on either the quantities or the prices. The price year used was 2000, which will facilitate any future reflation exercises.
Other issues	The authors made appropriate comparisons of their results with the findings from other studies. The issue of the generalisability to other settings was not addressed, although the authors pointed out that the surgeons in the study were all experienced in performing this kind of LAP. The authors did not present their results selectively, but their conclusions did not reflect the disadvantage of the non-randomised nature of the study and the lack of comparability of the patient groups. Also, the authors did not seem to be aware of the limited usefulness of the cost data that they provided.
Implications of the study	The authors concluded that LAP for patients with ileocecal Crohn's disease should become much more widely accepted as it leads to quicker recovery time and is less expensive. However, the comments made about the lack of randomisation, lack of long-term follow-up and lack of detailed cost data mean that more research is needed to confirm the authors' conclusions.
Source of funding	None stated.
Bibliographic detail	Duepree H J, Senagore A J, Delaney C P, Brady K M, Fazio V W. Advantages of laparoscopic resection for ileocecal Crohn's disease. Diseases of the Colon and Rectum 2002; 45(5): 605-610
Link to Pubmed record	12004208
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Adult; Cecum /surgery; Cohort Studies; Comparative Study; Costs and Cost Analysis; Crohn Disease /economics /surgery; Female; Humans; Intestinal Obstruction /surgery; Laparoscopy /economics /methods; Male; Middle Aged; Postoperative Complications; Statistics, Nonparametric; Treatment Outcome
Accession number	22002000953
Database entry date	31 May 2005
Record status	This is a critical structured abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Dupree 2002: HEED record

Article Reference No	065139
Author	Duepree H-J, Senagore A J, Delaney C P, Brady K M, Fazio V W
Article Title	Advantages of laparoscopic resection for ileocecal Crohn's disease
Journal Name	Diseases of the Colon and Rectum
Journal Date	2002
Journal Reference	45(5):605-610
Publication Status	Published in a peer reviewed journal
Availability Details	Reprints: Dr Senagore, Department of Colorectal Surgery, The Cleveland Clinic Foundation, Desk A-30, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA
First Year Clinical Data	1999
Last Year Clinical Data	2000
Cost Base Year	2000
Source Of Article	O
Countries Of Authors	USA
Countries Applicable	USA
Type Of Article	Applied study
Type Of Econ Eval	Cost consequences
Technology Assessed	Surgical;Procedures
ICD-9 Codes	569
Non-Drug Technologies Assessed	Laparoscopic vs open resection for ileocecal Crohn's disease
Prob. of Main Clinical Events	Observational data
Quantities of Resources Used	Observational data
Prices or Costs of Resources	Local Standard Costs
Outcomes	Observational data

Outcome Measure	complications, time to return to work
Costs Included	Hospital costs;Direct provider/purchaser costs
Study Question	The authors conducted a cost analysis based on a prospective observational study which compared laparoscopic resection and open resection for terminal ileal Crohn's disease between June 1 1999 and October 31, 2000. The setting was the Department of Colorectal Surgery at the Cleveland Clinic in Ohio; USA. The perspective was that of hospital provider. The cost analysis involved use of the hospital cost accounting system. Overhead costs were not included which would have accounted for 45 to 57% of the total cost.
Key Results	Three patients in the laparoscopic group had complications: anastomotic leak (n=1); intraabdominal abscess (n=1); and postoperative bleeding (n=1). In the open-resection group, two patients developed wound infections and two patients developed pulmonary atelectasis and fever. The laparoscopic patients returned to work earlier: 4 weeks (IQ range 3-6 weeks) compared to the open-resection patients; 6 weeks (IQ range 4-8 weeks). This difference was statistically significant at $p<0.05$). The direct cost for the laparoscopic group was $2,547 and for the open-resection group was $2,985. This difference was statistically significant at $p<0.05$. The authors concluded that laparoscopic resection for ileocecal Crohn's disease was cost-effective and shortened length of stay.
Patient Group	Patients with terminal ileal Crohn's disease. 24 underwent open surgery and 21 the laparoscopic-assisted approach. No patients had prior bowel resections or enterocutaneous fistulas. Median age 31 for the laparoscopic-assisted group and 39 for the open-group. 2 patients in the laparoscopic group were American Society of Anesthesiologists (ASA) classification 1; 17 were ASA classification 11 and 2 ASA classification 111. In the open group: 15 patients were ASA classification 11 and 9 patients ASA classification 111.
Keywords	Laparoscopic Surgery;Cost Consequences;Applied Study;Surgery;Procedures;Observational Data

Maartense 2006: NHS EED record

Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial
Maartense S, Dunker M S, Slors J F, Cuesta M A, Pierik E G, Gouma D J, Hommes D W, Sprangers M A, Bemelman W A

Health technology	The use of laparoscopic-assisted ileocolic resection for the treatment of Crohn's disease.
Type of intervention	Treatment.
Hypothesis/study question	The aim of this study was to compare the clinical effectiveness, quality of life and cost implications of laparoscopic-assisted ileocolic resection compared with open resection. This comparator appears to have been chosen as it represented usual practice in the authors' setting. The perspective of the economic analysis appears to have been that of the hospital.
Economic study type	Cost-effectiveness analysis.
Study population	The study population comprised adult patients requiring ileocolic resection for Crohn's disease.
Setting	The setting was secondary care. The economic study was carried out in the Netherlands.
Dates to which data relate	The clinical effectiveness and resource use data were collected between 2000 and 2003. No price year was reported.
Source of effectiveness data	The effectiveness data were derived from a single study.
Link between effectiveness and cost data	The cost data were collected from the same patient sample that provided the clinical effectiveness evidence.
Study sample	Sample size calculations were reported. These indicated that the study had the power to detect a 20% difference between the two patient groups. Patients were recruited to the trial in the outpatient department. The study comprised 60 patients, of which 30 were in the laparoscopic resection group and 30 in the open resection group. Two patients were excluded from the study as they refused to be randomised to treatment.
Study design	The study was a multi-centre randomised controlled trial that involved three hospitals. The patients were randomised using sealed envelopes. There was no blinding of the patients or professionals to the treatment given. The patients were followed up for 3 months after surgery. Eight patients did not provide any postoperative quality of life data. This loss to follow-up was equal in both patient groups.
Analysis of effectiveness	The analysis of the study data was conducted on an intention to treat basis. The primary health outcome was quality of life, as measured by the SF-36 and Gastro-Intestinal Quality of Life Index (GIQLI). Other outcomes were operating times, length of hospital stay, morphine requirements, time to returning to normal diet, and complications and readmissions 30 days post surgery. The two patient groups were shown to be comparable at baseline.

Effectiveness results	There were no statistically significant differences in postoperative SF-36 and GIQLI scores between the two patient groups. The mean operating time was 115 minutes (range: 70 to 255) in the laparoscopic group compared with 90 minutes (range: 30 to 160) in the open surgery group, (p=0.003). The mean hospital stay was 5 days (range: 3 to 13) in the laparoscopic group compared with 7 days (range: 4 to 12) in the open surgery group, (p=0.008). Three patients in the laparoscopic group and eight in the open surgery group had minor complications in the 30 days post surgery. One patient in the laparoscopic group and four in the open surgery group had major complications in the 30 days post surgery. No patients in the laparoscopic group but four in the open surgery group were readmitted within 30 days. The morphine requirement was lower in the laparoscopic group than in the open surgery group (mean 29 mg versus 62 mg; p=0.27). The mean time to return to normal diet was 4 days (range: 2 to 7) in the laparoscopic group compared with 4 days (range: 3 to 10) in the open surgery group, (p=0.003).
Clinical conclusions	The authors concluded that, compared with open surgery, laparoscopic ileocolic resection for Crohn's disease results in reduced morbidity and hospital stay.
Measure of benefits used in the economic analysis	No measure of health benefit was combined with the cost data. Therefore, a cost-consequences study was performed.
Direct costs	The direct costs of the hospital were included in this study. The resource use data were taken from the same patient sample that provided the clinical effectiveness data. The unit costs were taken from one of the hospitals participating in the study. Details of resource use, but not unit costs, were provided in the paper. No price year was reported.
Indirect Costs	No indirect costs were included in the study.
Currency	Euros (EUR).
Statistical analysis of costs	The differences in costs between the two patient groups were tested using Mann-Whitney tests.
Sensitivity analysis	No sensitivity analysis was undertaken.
Estimated benefits used in the economic analysis	See the 'Effectiveness Results' section.
Cost results	The median total cost was EUR 6,412 (range: 4,195 to 35,569) in the laparoscopic resection group compared with EUR 8,196 (range: 4,964 to 19,018) in the open surgery group, (p=0.042).
Synthesis of costs and benefits	Not relevant.

Authors' conclusions	There was no clear difference in clinical outcomes between laparoscopic and open resection, but laparoscopic resection had lower costs.
CRD COMMENTARY - Selection of comparators	The authors compared laparoscopic ileocolic resection with open ileocolic resection for Crohn's disease. No explicit rationale for this choice was reported in the paper, but it would appear that open surgery was usual practice in the authors' setting. You should consider how this relates to usual practice in your own setting before applying the results of this study.
Validity of estimate of measure of effectiveness	The measure of clinical effectiveness was taken from a randomised controlled trial, which is appropriate for the study question. Although it was not practical to blind the patients or health care professionals to the type of surgery, it is possible that this might have introduced some bias into the trial. The two patient groups were shown to be comparable at baseline. However, the authors did not compare their sample with the wider patient population, so it is not clear whether the sample was representative. An appropriate statistical analysis was undertaken on an intention to treat basis.
Validity of estimate of measure of benefit	No measure of health benefit was combined with the cost data. Therefore, a cost-consequences study was performed.
Validity of estimate of costs	The hospital costs were identified in this study. The paper did not provide a breakdown of the individual costs included in the study, so it was not clear whether all the appropriate costs were included. No statistical or sensitivity analysis was undertaken, which means that the extent of uncertainty around the cost data was not taken into consideration. A breakdown of resource use and unit costs was not provided, and the source of the unit costs was not reported. These factors reduce the generalisability of the study findings. No price year was reported, which will prevent any future reflation exercises.
Other issues	The authors do not appear to have presented their results selectively and their conclusions reflected their analysis. They did not consider how their findings could be generalised to other settings. However, they compared their results with other relevant studies and discussed the differences between them.
Implications of the study	The authors did not make any recommendations for further research or changes to practice. However, the findings support the use of laparoscopic-assisted ileocolic resection from both effectiveness and economic perspectives.
Source of funding	None stated.
Bibliographic detail	Maartense S, Dunker M S, Slors J F, Cuesta M A, Pierik E G, Gouma D J, Hommes D W, Sprangers M A, Bemelman W A. Laparoscopic-assisted versus open ileocolic resection for Crohn's disease: a randomized trial. Annals of Surgery 2006; 243(2): 143-149
Link to Pubmed record	16432345
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Adolescent; Adult; Chi-Square Distribution; Comparative Study; Crohn Disease /surgery; Digestive System Surgical Procedures /methods; Female; Hospital Costs; Humans; Ileum; Laparoscopy; Length of Stay /statistics & numerical data; Male; Middle Aged; Netherlands; Postoperative Complications; Prospective Studies; Quality of Life; Statistics, Nonparametric; Treatment

	Outcome
Accession number	22006000661
Database entry date	31 March 2007
Record status	This is a critical structured abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Maartense 2006: HEED record

Article Reference No	015463
Author	Maartense S, Dunker M S, Slors J F, Cuesta M A, Gouma D J, van Deventer S J, van Bodegraven A A, Bemelman W A
Article Title	Hand-assisted laparoscopic versus open restorative proctolectomy with ileal pouch anal anastomosis û a randomized trial
Journal Name	Annals of Surgery
Journal Date	2004
Journal Reference	240(6):984-992
Publication Status	Published in a non peer reviewed journal
Availability Details	Reprints: Willem A Bemelman, MD, Department of Surgery, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. E-mail: W.A.Bemelman@amc.uva.nl
First Year Clinical Data	2000
Last Year Clinical Data	2000
Cost Base Year	2000
Source Of Article	O
Countries Of Authors	The Netherlands
Countries Applicable	The Netherlands
Type Of Article	Applied study
Type Of Econ Eval	Cost consequences
Technology Assessed	Surgical;Procedures
ICD-9 Codes	556
Non-Drug Technologies Assessed	Hand-assisted laparoscopic, open restorative proctocolectomy with ileal pouch anal anastomosis
Prob. of Main Clinical Events	Randomised clinical trial
Quantities of Resources Used	Randomised clinical trial
Prices or Costs of Resources	National Publication
Outcomes	Randomised clinical trial
Outcome Measure	Quality of life
Qual Of Life Index	Generic;Disease specific;SF-36 and GIQLI
Costs Included	Hospital costs;Direct provider/purchaser costs;Indirect costs
Study Question	The main objective of this paper was to evaluate postoperative recovery in terms of quality of life after hand-assisted laparoscopic or open restorative proctocolectomy with IPAA for UC and FAP in a randomized controlled trial. The primary outcome measure was postoperative recovery in the 3 months after surgery, measured by

	quality of life questionnaires (SF-36 and GIQLI), and the secondary outcome measures were postoperative morphine requirement and surgical parameters such as operating time, morbidity, hospital stay, and costs.
Key Results	This study is believed to be the first randomized controlled trial that compares hand-assisted laparoscopic versus open restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) for patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP). The authors found that postoperative quality of life was not different for the laparoscopic procedure compared with the open procedure as measured by the SF-36 and the GIQLI. Quality of life decreased significantly immediately after surgery. In the present study, quality of life levels were back at the baseline after 4 weeks. Three months after surgery, quality of life had improved in comparison to the preoperative levels of all scales of the SF-36 and the total GIQLI score. However, this improvement was not significant. Results of this study indicate that in centers with expertise it can be offered safely to the patients. Median overall costs for hand-assisted laparoscopic procedure was Euros 16,728 and for open procedure Euros 13,406 ($p = 0.095$).
Patient Group	Patients eligible for an elective proctocolectomy with ileal pouch anal anastomosis (IPAA) for ulcerative colitis (UC) or familial adenomatous polyposis (FAP) were included in a randomized trial.
Keywords	Surgery;Quality of Life;Laparoscopy;Applied Study;Post Operative Care;Randomised Clinical Trial;Hospital Care;Direct Costs;Indirect Costs;Cost Consequences Analysis

Msika 2001: NHS EED record

N/A – Not identified in search of NHS EED

Msika 2001: HEED record

Article Reference No	042122
Author	Msika S, Iannelli A, Deroide G, Jouet P, Soule J-C, Kianmanesh R, Perez N, Flamant Y, Fingerhut A, Hay J-M
Article Title	Can laparoscopy reduce hospital stay in the treatment of Crohn's disease?
Journal Name	Diseases of the Colon and Rectum
Journal Date	2001
Journal Reference	44(11):1661-1666
Publication Status	Published in a peer reviewed journal
Availability Details	Reprints: Dr Msika, Service de Chirurgie Digestive, Centre Hospitalo-Universitaire Louis Mourier (Assistance Publique, H_pitaux de Paris), 178 rue des Renouillers, 92700 Colombes, France
First Year Clinical Data	1996
Last Year Clinical Data	2000
Source Of Article	O
Countries Of Authors	France
Countries Applicable	France
Type Of Article	Applied study
Type Of Econ Eval	Cost consequences
Technology Assessed	Surgical;Procedures
ATC Codes	N01A
ICD-9 Codes	564
Non-Drug Technologies Assessed	Laparoscopy or open surgery
Prob. of Main Clinical Events	Observational data
Quantities of Resources Used	Observational data
Prices or Costs of Resources	Local Standard Costs
Outcomes	Observational data
Outcome Measure	Length of stay, safety, outcome,
Costs Included	Hospital costs;Direct provider/purchaser costs
Study Question	The aim of this study was to investigate the safety, outcome, length of stay, and cost of hospital admission in patients with Crohn's disease who underwent laparoscopy compared with open surgery. This was done through a study undertaken at a hospital in France. The study was undertaken from the perspective of the hospital.

Key Results	The OG group comprised 26 patients, mean age 41.8 years, 11 males, 15 females. Mean (_ sd) duration of the disease was 11.6 _ 7.6 years mean BMI was 20.6 _ 3.68. 17 had previous abdominal surgery, 22 had CrohnÆs disease, 3 had no preoperative medical treatment, 21 had corticosteroids and 16 Azathioprin. The LG group comprised 20 patients, mean age 38 years, 7 males, 13 females. Mean (_ sd) duration of the disease was 7.2 _ 6.2 years mean BMI was 20.4 _ 1.86. 10 had previous abdominal surgery, 15 had CrohnÆs disease, 2 had no preoperative medical treatment, 18 had corticosteroids and 12 Azathioprin. There was no significant difference between the groups. There was no significant difference in the type of procedure performed, with ileocolectomy the most frequent procedure in both groups. There was no mortality. There was no intraoperative complication in either group and no conversion in the laparoscopic group. Operating time was significantly longer in the laparoscopic group (302 minutes) vs. the open group (244.7 minutes) ($P < 0.05$), but this difference disappeared when data were adjusted for the extra time required to perform the laparoscopic hand-sewn anastomoses (288.2 minutes vs. 244.7 minutes). Bowel function returned more quickly in the laparoscopic group vs. the open group in terms of passage of flatus (3.7 vs. 4.7 days) ($P < 0.05$) and resumption of oral intake (4.2 vs. 6.3 day) ($P < 0.01$). There were significantly fewer postoperative complications in the laparoscopic group (9.5 percent) vs. the open group (18.5 percent) ($P < 0.05$); the length of stay was significantly shorter in the laparoscopic group (8.3 days) vs. the open group (13.2 days) ($P < 0.01$); and the cost of hospital admission was significantly lower in the laparoscopic group ($6106 vs. the open group $9829 ($P < 0.05$)). Five patients (18.5%) experienced post-operative complications in the OG group and 2 (9.5%) in the LG group ($p<0.05$). Mean follow-up tiem was 30 (2.6-53) months in the OG group and 10 (1.5-23) in the LG group, with no anastomatic complications or clinical recurrences. The authors conclude that there is a reduction in the postoperative ileus, length of stay, cost of hospital admission, and postoperative complication rate in the laparoscopic group.
Patient Group	51 consecutive patients undergoing elective surgery for inflammatory bowel disease (IBD), of which 46 with CrohnÆs disease were included in the study. 20 underwent laparoscopic intestinal surgery (LG) and 26 traditional open surgery (OG)
Keywords	Applied Study;Cost Consequences;Costs;Crohn's Disease;Inflammatory Bowel Disease;Laparoscopic Surgery;Observational Data;Outcomes;Surgery

Scarpa 2009: NHS EED record

N/A – Not identified in search of NHS EED

Scarpa 2009: HEED record

Article Reference No	059818
Author	Scarpa M, Ruffolo C, Bassi D, Boetto R, D'Inca R, Buda A, Sturniolo G C, Angriman I
Article Title	Intestinal surgery for Crohn's disease: predictors of recovery, quality of life, and costs
Journal Name	Journal of Gastrointestinal Surgery
Journal Date	2009
Journal Reference	13:2128û2135
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence to: M. Scarpa, Department of Oncological Surgery, Veneto Oncological Institute, via Gattamelata 74, 35128 Padova, Italy. E-mail: marcoscarpa73@yahoo.it
First Year Clinical Data	2006
Last Year Clinical Data	2008
Cost Base Year	2008
Source Of Article	O
Countries Of Authors	Italy
Countries Applicable	Italy
Type Of Article	Applied study
Type Of Econ Eval	Cost analysis
Technology Assessed	Surgical
ICD-9 Codes	569
Non-Drug Technologies Assessed	Surgical procedures for Chron's disease (CD)
Prob. of Main Clinical Events	Observational data;Modelling
Quantities of Resources Used	Observational data
Prices or Costs of Resources	National Publication
Outcomes	Observational data;Modelling
Outcome Measure	Disability status, quality of life, body image, disease activity
Qual Of Life Index	Disease specific;Cleveland Global Quality of Life score
Costs Included	Hospital costs;Direct provider/purchaser costs;Indirect costs
Study Question	The aim of this prospective cohort study was to analyze the impact of different surgical techniques on patients undergoing intestinal surgery for CrohnÆs disease (CD) in terms of recovery, quality of life, and direct and indirect costs. In the analysis, surgical procedures such as laparoscopic-assisted bowel resection,

	stricturoplasty, stoma creation, ileal resection, and colonic resection as well as clinical predictors, such as age, gender, CD duration, activity and localization, and recurrent CD were evaluated. Outcomes of interest were disability status, quality of life, body image, and disease activity. Multiple linear regression models were constructed with predictors that were found to be significant on univariate analysis to assess the different role of each one. When the number of predictors exceeded 5, stepwise forward regression analysis was used. Both univariate and multivariate regression analyses were performed. The study setting was secondary care in Italy and the economic perspective was that of society.
Key Results	The results showed that significant predictors of a long postoperative hospital stay were the creation of a stoma, postoperative complications, disability status on the third post-operative day, and surgical access (R2=0.59, p<0.01). BarthelÆs index at discharge was independently predicted by laparoscopic-assisted approach, ileal CrohnÆs disease (CD), and colonic CD (R2=0.53, p<0.01). The disability status at admission was shown to be an independent predictor of quality of life score at follow-up. The overall cost for intestinal surgery for CD was 12,037 (10,117û15,795) euro per patient and stoma creation was revealed to be its only predictor (p=0.006). Patients who had laparoscopic-assisted bowel resection reported significantly lower costs for the hospital stay (p=0.021), but the overall costs were not different compared for patients who had open surgery. The authors concluded that laparoscopy was associated with a shorter postoperative length of stay; stoma creation was associated with a long and expensive postoperative hospital stay, and stricturoplasty was associated with a slower recovery of bowel function.
Patient Group	47 consecutive patients (51% male, median age 38 [31-54]) admitted for intestinal surgery for CrohnÆs disease (CD) were enrolled into the study. Diagnosis of CD was made with clinical, endoscopic, and blood tests according to LennardûJones criteria. Patients who were admitted for surgery for perineal CD were excluded because of the different surgical procedures and the important impact on quality of life of this disease location.
Sponsor	Government/publicly funded policy making body
Keywords	Bowel - Gastrointestinal Disorders;Bowel - Surgery;Cost Analysis;Crohn's Disease;Surgery - Bowel;Surgery - Laparoscopic

Shore 2003: NHS EED record

Laparoscopic vs conventional ileocolectomy for primary Crohn disease.
Shore G, Gonzalez Q H, Bondora A, Vickers S M

Record status	This study has been evaluated by a health economist for CRD and is considered to be a partial economic evaluation. Partial economic evaluations are studies that meet CRD's broad inclusion criteria as a full economic evaluation, but which only report highly summarised cost or effectiveness results. This category includes papers that report only the total costs of the interventions or cost minimisation studies which rely on equivalence of effects established elsewhere in the literature.
Bibliographic detail	Shore G, Gonzalez Q H, Bondora A, Vickers S M. Laparoscopic vs conventional ileocolectomy for primary Crohn disease. Archives of Surgery 2003; 138(1): 76-79
Link to Pubmed record	12511156
Language	English
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Adolescent; Adult; Aged; Cecum /surgery; Colectomy /economics /methods; Comparative Study; Crohn Disease /economics /surgery; Digestive System Surgical Procedures /economics /utilization; Female; Hospital Charges /statistics & numerical data; Hospitals, University /economics /utilization; Humans; Ileum /surgery; Laparoscopy /economics /utilization; Length of Stay /economics /statistics & numerical data; Male; Middle Aged; Outcome and Process Assessment (Health Care); Recurrence; Retrospective Studies; United States
Accession number	22003006147
Database entry date	17 June 2003

Shore 2003: HEED record

N/A – Not identified in search of HEED

Young-Fadok 2001: NHS EED record

Advantages of laparoscopic resection for ileocolic Crohn's disease: improved outcomes and reduced costs

Young-Fadok T M, Long K H, McConnell E J, Rey G G, Cabanela R L

Health technology	Laparoscopic ileocolic resection (LAP), the alternative technology, was compared with open ileocolic resection (OPEN). The authors reported that the technique of laparoscopic-assisted ileocecal resection or right hemicolectomy had been described before (Young-Fadok et al., see 'Other Publications of Related Interest' for bibliographic details).
Type of intervention	Treatment.
Hypothesis/study question	The authors reported that the study was undertaken to test the following hypotheses: that LAP for a diagnosis of Crohn's disease (CD) is feasible; that patients experience improved postoperative outcomes compared with those undergoing the comparable open procedure; and that the costs are reduced with the laparoscopic approach. The authors stated that the specific aims were to determine the conversion rate in a series of patients undergoing LAP for CD and to compare the postoperative outcomes of patients undergoing LAP versus OPEN. Also, to perform a formal cost analysis of the laparoscopic versus open groups. OPEN was clearly the comparator in this study, but relevant details were not given in this paper. It was reported that studies of laparoscopic colorectal procedures had demonstrated the feasibility of this approach in large series performed for multiple indications. However, the authors reported that there was a lack of consensus about the magnitude of the associated benefits. The authors chose to study a single procedure performed for a single indication. It would appear that they hoped that findings from this focused study would add to the available pool of knowledge and thus assist in forming a consensus on the merits of this approach. The authors stated that the economic analysis was conducted from a societal perspective.
Economic study type	Cost-effectiveness analysis.
Study population	The patient population appears to have been made up of patients requiring LAP for CD (drawn from the laparoscopic colorectal database) and those undergoing OPEN (identified from the Mayo Clinic Surgical Index).
Setting	The setting was secondary care. The economic study appears to have been carried out in Minnesota, USA.
Dates to which data relate	The laparoscopic resections were performed between October 1995 and July 1999. It was unclear when the open laparotomy resections were performed but it was stated that cases were matched for date of operation +/- 2 years, so the bounds for the date of operation for the OPEN group are October 1993 and July 2001. However, it should be noted that this paper was received by the publishers in June 2001. It would appear that the resource use data were collected for the same time period (i.e. October 1995 to June 2001). The price year was 1999.

Source of effectiveness data	The effectiveness data were derived from a single study.
Link between effectiveness and cost data	The costing, which appears to have been undertaken retrospectively, seems to have been carried out on the same patient sample as that used in the effectiveness study.
Study sample	Power calculations were not reported to have been carried out. The study sample was made up of two groups of patients. First, the laparoscopic colorectal database (LAP group) was used to identify 33 consecutive cases of laparoscopic resection of ileocolic or terminal ileal CD performed between October 1995 and July 1999. Once this group had been identified, a case-match methodology was used to identify open laparotomy controls (OPEN group) from the Mayo Clinic Surgical Index. The controls were matched for age (+/- 5 years), gender, diagnosis (CD), type of resection (ileocecectomy and right hemicolectomy) and date of operation (+/- 2 years). The authors did not justify their sample with respect to the characteristics of the disease or the treatment under investigation. However, they did justify their choice of matching criteria and explained that matching for age and gender are standard approaches. The date of the operation was used in an attempt to control for changes in postoperative practice that occur over time, and to control for the known reduction in hospital stay that has also occurred in recent years. Matching for both procedure and indication was aimed at eliciting benefits, if present, in a specific group of patients. However, it would appear that matching for procedure and indication would limit the generalisability of results.
Study design	This was a case-match study which appears to have been conducted in a single centre, the Mayo Clinic, Minnesota, USA. The follow-up period appears to have been the length of hospital stay, which ranged from 2 to 14 days. There was no reported loss to follow-up.
Analysis of effectiveness	The analysis of effectiveness was conducted on an intention to treat basis. The primary health outcomes were: the number of days to clear liquids, the number of days to regular diet, shifts of narcotics, operating time, intraoperative complications, postoperative complications, and length of stay. The authors reported that the process of matching resulted in identical distributions of gender, age and date of operation in the two groups, although those in the LAP group had a slightly higher body mass index than those in the OPEN group. A comparison of potentially confounding non-matched criteria confirmed that there were no statistically significant differences in perioperative steroids and prior abdominal operation. Also, the American Society of Anesthesiologists' status was not statistically different between the groups.
Effectiveness results	The operating time was 147 minutes (range: 82 - 235) for the LAP group and 124 minute (range: 35 - 258) in the OPEN group, (p=0.05).

	There were no intraoperative complications in either group, nor were there significant differences in postoperative complication rates. The median number of days to clear liquid was 0 (range: 0 - 4) in the LAP group and 3.0 (range: 2 - 8) in the OPEN group, (p=0.0001). The median number of days to regular diet was 2.0 (range: 1 - 6) in the LAP group and 5.0 (range: 3 - 12) in the OPEN group, (p=0.0001). The median number of shifts to narcotics was 6.0 (range: 2 - 14) in the LAP group and 10.0 (range: 3 - 34) in the OPEN group, (p=0.001). The median length of stay was 4.0 (range: 2 - 8) in the LAP group and 7.0 (range: 3 - 14) in the OPEN group, (p=0.0001).
Clinical conclusions	The authors concluded that laparoscopic ileocolic resection for CD is feasible. In addition, there are significant postoperative benefits in terms of ileus, narcotic use and hospital stay.
Measure of benefits used in the economic analysis	The authors did not derive a summary measure of health benefit. In effect, a cost-consequences analysis was performed.
Direct costs	The resource quantities were not reported. The direct costs included in the analysis were those of the health care provider (i.e. the hospital). These were the costs of the room and board, medication, supplies, operating room and anaesthesia. The authors reported that the costing process was facilitated by the use of the Olmsted County Healthcare Expenditure and Utilization Database (OCHEUD), a system that provides a standardised inflation-adjusted estimate of the cost of each service or procedure in 1999 constant dollars. They explained that this system uses a micro-costing approach. Resource use was grouped into the Medicare Part A and B classification system. Part A billed charges were adjusted using hospital cost-to-charge ratios, while Part B physician services were adjusted using 1999 Medicare reimbursement rates. There was no report of models being used to extrapolate to a longer timeframe or another setting. Discounting was not relevant. The study reported both the mean and median costs.
Indirect Costs	A rationale for the inclusion or exclusion of productivity costs was not given. The study only considered the loss of working days associated with hospital length of stay. The source of the cost data was the average hourly wage rates taken from the Bureau of Labor Statistics Current Population Survey (see 'Other Publications of Related Interest' for bibliographic details). Quantities, as median and mean length of hospital stay for each patient group, were reported separately from the combined figures for the mean and median indirect costs for the two groups. Only indirect patient costs were considered. The quantities were estimated from actual data. The authors reported that the indirect costs were valued using standard methods based on gender- and age-specific average hourly wage rates. The resource quantities were measured when the effectiveness data were collected (i.e. October 1995 to June 2001). Discounting was not relevant. The price data related to 1999.
Currency	US dollars ($).
Statistical analysis of costs	The cost data were presented as a mean with 95% confidence interval (CI). The median cost was also reported. Outcomes were reported as the mean and range. The authors reported that the outcomes for the matched patient pairs were analysed using sign and signed rank tests. Intra-pair mean differences

	(laparoscopic minus open) in the total costs, direct costs and indirect costs were compared using standard t-tests. Further, the robustness of these standard tests of significance in the presence of skewed data and the variability in estimated costs were determined using non-parametric bootstrapping techniques. The authors pointed out that the bootstrapped estimates of the intra-pair mean difference in costs indicated that the study sample size was sufficient for robust t-tests of significance.
Sensitivity analysis	No sensitivity analysis was reported.
Estimated benefits used in the economic analysis	See the 'Effectiveness Results' section.
Cost results	The mean direct costs for room and board were $2,412 (95% CI: 2,055 - 2,856) for the LAP group and $4,751 (95% CI: 3,826 - 5,097) for the OPEN group. The intra-pair difference was -$2,339 (95% CI: -2,735 - -1,273), (p<0.001). The median costs for room and board were $2,098 (LAP) and $4,238 (OPEN), respectively, and the intra-pair difference was -$2,078. The mean direct costs for medications were $955 (95% CI: 829 - 1,028) for the LAP group and $1,762 (95% CI: 1,459 - 2,086) for the OPEN group. The intra-pair difference was -$808 (95% CI: -1,185 - -485), (p<0.001). The median costs for medication were $896 (LAP) and $1,489 (OPEN), respectively, and the intra-pair difference was -$635. The mean direct costs for supplies were $1,057 (95% CI: 887 - 1,185) for the LAP group and $599 (95% CI: 526 - 719) for the OPEN group. The intra-pair difference was $458 (95% CI: 228 - 625), (p<0.001). The median costs for supplies were $1,002 (LAP) and $591 (OPEN), respectively, and the intra-pair difference was $378. The mean direct costs for the operating room were $1,799 (95% CI: 1,668 - 1,846) for the LAP group and $1,597 (95% CI: 1,479 - 1,640) for the OPEN group. The intra-pair difference was $202 (95% CI: 84 - 305), (p=0.003). The median costs for the operating room were $1,386 (LAP) and $1,566 (OPEN), respectively, and the intra-pair difference was $197. The mean direct costs for anaesthesia were $508 (95% CI: 475 - 540) for the LAP group and $453 (95% CI: 416 - 465) for the OPEN group. The intra-pair difference was $56 (95% CI: 29 - 110), (p=0.010). The median costs for anaesthesia were $504 (LAP) and $443 (OPEN), respectively, and the intra-pair difference was $48. The mean total direct costs were $8,684 (95% CI: 7,931 - 9,296) for the LAP group and $11,373 (95% CI: 9,986 - 12,031) for the OPEN group. The intra-pair difference was -$2,690 (95% CI: -3,514 - -1,246), (p<0.001). The median total direct costs were $8,029 (LAP) and $10,527 (OPEN), respectively, and the intra-pair difference was -$2,138. The mean total indirect costs were $1,358 (95% CI: 1,149 - 1,637) for the LAP group and $2,349 (95% CI: 2,054 - 2,785) for the OPEN group. The intra-pair difference was -$991 (95% CI: -1,397 - -620), (p<0.001). The median total indirect costs were $1,213 (LAP) and $2,037 (OPEN), respectively, and the intra-pair difference was -$836. The mean total costs were $9,895 (95% CI: 9,205 - 10,905) for the LAP group and $13,268 (95% CI: 12,218 - 14,762) for the OPEN group. The intra-pair difference was -$3,373 (95% CI: -4,922 - -1,918), (p<0.001). The median total costs were $9,158 (LAP) and $12,896 (OPEN), respectively, and the intra-pair

	difference was -$2,725. The costs of adverse effects and knock-on costs were not reported.
Synthesis of costs and benefits	The costs and benefits were not combined.
Authors' conclusions	Laparoscopic resection for ileocolic Crohn's disease (CD) is feasible and has both patient benefits and cost advantages in comparison with open resection. These cost advantages were seen in the analysis of both the direct and indirect costs, resulting in an average cost-difference of greater than $3,300 in favour of laparoscopic resection.
CRD COMMENTARY - Selection of comparators	Although no explicit justification was given for the comparator used, it would appear to represent current practice in the authors' setting. You should decide if the comparator represents current practice in your own setting.
Validity of estimate of measure of effectiveness	The authors justified their choice of design by explaining that they were unable to carry out a randomised trial, which would have been their preferred option. This was because they believed that even if investigators were uncertain of the relative merits of the two arms, they feared that the patients' views on the benefits of one technology (usually laparoscopy) would lead to a refusal to consider randomisation. They felt that a matched pair study design was the best option available to them. The study sample was made up of the whole study population and can thus be considered to be representative. The patient groups were shown to be comparable at analysis. The analysis of effectiveness appears to have been handled credibly.
Validity of estimate of measure of benefit	The authors did not derive a summary measure of health benefit. The study was, in effect, a cost-consequences analysis.
Validity of estimate of costs	It appears that all the cost categories relevant to the perspective adopted have been included in the analysis. The indirect cost associated with the time between leaving hospital and returning to work was not included in the analysis. The authors stated that, as it is likely that the decreased recuperative time translates into a faster return to full work capacity, the cost analysis (as completed) was a conservative estimate of the savings in indirect costs in favour of the LAP approach. The resource use quantities were not reported. Sensitivity analyses of the prices were not conducted, nor were any further analyses of the prices. The authors reported that the use of the OCHEUD costing system meant that charges were not used to proxy prices. The date to which the price data related (1999) was reported.
Other issues	The authors made appropriate comparisons of their results with the findings of other studies. However, the issue of generalisability to other settings was not addressed. The authors do not appear to have presented their results selectively. In terms of the procedure and the indication, the authors' conclusions reflected the scope of the study. No further limitations were reported.
Implications of the study	No specific implications were reported.
Source of funding	None stated.
Bibliographic detail	Young-Fadok T M, Long K H, McConnell E J, Rey G G, Cabanela R L. Advantages of laparoscopic resection for ileocolic Crohn's disease: improved

	outcomes and reduced costs. Surgical Endoscopy - Ultrasound and Interventional Techniques 2001; 15(5): 450-454
Other publications of related interest	Young-Fadok TM, Nelson H. laparoscopic right colectomy: five-step procedure. Diseases of the Colon and Rectum 2000;43:267-73. US Department of Labor, Bureau of Labor Statistics. Median usual weekly earnings of full-time wage and salary workers by age, race, Hispanic origin, and sex, fourth quarter 1999 averages, not seasonally adjusted (Table 2). Labor Force Statistics from the Current Population Survey (online) 1999 (accessed 2000, Feb 10). Available from the following url: http://www.bls.gov
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Adolescent; Adult; Aged; Body Mass Index; Case-Control Studies; Colectomy /economics /methods; Colitis /surgery; Costs and Cost Analysis; Crohn Disease /economics /surgery; Feasibility Studies; Female; Humans; Ileitis /surgery; Laparoscopy /economics /methods; Length of Stay; Male; Middle Aged; Treatment Outcome
Accession number	22001001087
Database entry date	30 November 2005
Record status	This is a critical structured abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Young-Fadok 2001: HEED record

Article Reference No	013697
Author	Young-Fadok T M, Hall Long K, McConnell E J, Gomez Rey G, Cabanela R L
Article Title	Advantages of laparoscopic resection for ielocolic Crohn's disease: improved outcomes and reduced costs
Journal Name	Surgical Endoscopy
Journal Date	2001
Journal Reference	15:450-454
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence: T M Young-Fadok, Division of Colon and Rectal Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA
First Year Clinical Data	1995
Last Year Clinical Data	1999
Cost Base Year	1999
Source Of Article	O
Countries Of Authors	USA
Countries Applicable	USA
Type Of Article	Applied study
Type Of Econ Eval	Cost analysis
Technology Assessed	Surgical;Diagnostic
ICD-9 Codes	555
Prob. of Main Clinical Events	Observational data
Quantities of Resources Used	Observational data
Prices or Costs of Resources	Local Standard Prices
Costs Included	Hospital costs;Direct provider/purchaser costs
Study Question	The study tested the hypothesis that laparoscopioc ileocolic resection for a diagnosis of Crohn¦s disease is feasible, that patients experience improved postoperative outcomes compared with individuals undergoing the comparable open procedure, and that costs are reduced with the laparoscopic approach. The conversion rate was determined in patients undergoing laparoscopic ileocolic resection for Crohn¦s disease, as well as the postoperative outcomes of patients undergoing laparoscopic vs open ileocolic resection and costs.
Key Results	The economic and clinical advantages of laparoscopic resection for ileocolic Crohn¦s disease (CD) were determined in this paper, using

	a case-match methodology. 33 cases of laparoscopic resection of ileocolic or terminal ileal CD and 33 cases of open laparotomy controls were identified. Significant reductions in direct costs were seen in the laparoscopic group when compared to the open laparotomy group ($8684 versus $11373, p < 0.001), and specifically in terms of hospital length of stay ($1358 versus 2349, o < 0.001). This resulted in a total cost reduction of $9895 versus $13268 (p < 0.001). In terms of patient¦s benefits, resolution of ileus occurred more rapidly in the laparoscopic group (0 days range, 0-4) than in the open laparatomy group (3.0 days range, 2-8 days) (p = 0.0001), and hospital stay was also reduced (4.0 days versus 7.0 days) (p = 0.0001).
Patient Group	33 consecutive cases (male:female ratio 21:12 in each group; age mean, 37.3 years) of laparoscopic resection of ileocolic or terminal ileal Crohn¦s disease (CD).
Keywords	Applied Study;Colorectal - Neoplastic Disease;Cost Analysis;Crohn's Disease;Diagnostic Procedures;Direct Costs;Laparoscopic Surgery;Observational Data;Surgery - Colorectal

Wildschut 2011: Economic evaluation

Ngai 2000: NHS EED record

N/A – Not identified in search of NHS EED

Ngai 2000: HEED record

Article Reference No	028227
Author	Ngai S W, Tang O S, Ho P C
Article Title	Randomized comparison of vaginal (200 ug verey 3 h) and oral (400 ug every 3 h) misoprostolwhen combined with mifepristone in termination of second trimester pregnancy
Journal Name	Human Reproduction
Journal Date	2000
Journal Reference	15:2205-2208
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence: Suk Wai Ngai, Dept of Obstetrics and Gynaecology, University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong SAR, China
Source Of Article	O
Countries Of Authors	Hong Kong
Countries Applicable	Hong Kong
Type Of Article	Applied study
Type Of Econ Eval	Cost consequences
Technology Assessed	Pharmaceutical
ICD-9 Codes	635
Prob. of Main Clinical Events	Randomised clinical trial
Quantities of Resources Used	Randomised clinical trial
Prices or Costs of Resources	Local Standard Costs
Outcomes	Randomised clinical trial
Outcome Measure	abortions completed within 24 hours
Costs Included	Hospital costs
Study Question	This paper reports the results of a randomized study which tested the hypothesis that oral misoprostol 400 microg is as effective as vaginal misoprostol 200 microg when given every 3 hours in the termination of second trimester pregnancy following initial priming with mifepristone. Patients were randomly assigned to either 200 mg mifepristone + 400 mg oral misoprostol every 3 h up to five doses, or to 200 mg mifepristone + 200 microg vaginal misoprostol every 3 h up to five doses). The main outcome measure being completed abortions after 24 hours. The additional costs of using oral misoprostol are reported.
Key Results	In terms of side-effects the incidence of diarrhoea was higher in the oral group, 40.0% of patients versus 23.2% (P = 0.03). The amount of misoprostol used in the oral group was also higher, 1734 mg vs. 812 ug (P < 0.0001) The complete abortion rate was 81.4% in the

	oral group vs.75.4% in the vaginal group, a non-significant difference. The overall proportion of women who aborted in 24 h was non-significantly different, 57/70 (81.4%) in the oral group and 58/69 (87.0%) in the vaginal group. In total 82.0% of women stated that they preferred the oral route. In Hong Kong one tablet of 200 ug of cost HK$2.10, the increase in drug cost by using oral misoprostol instead of vaginal was HK$9.68. It was concluded that the use of oral misoprostol (400 ug) given every 3 h up to five doses, when combined with mifepristone, was as effective as the vaginal (200 ug) route in second trimester termination of pregnancy.
Patient Group	Healthy pregnant women aged 16-35 years requesting legal second trimester termination of pregnancy (n = 142)
Keywords	Abortion;Cost Consequences;Pharmaceutical

Komossa 2011: Economic evaluations

Beard 2006: NHS EED record

A decision model to compare health care costs of olanzapine and risperidone treatment of schizophrenia in Germany

Beard A M, Maciver F, Clouth J, Ruther E

Health technology	The study compared the use of olanzapine with risperidone in the treatment of patients with an established history of schizophrenia.
Type of intervention	Treatment.
Hypothesis/study question	The objective of the study was to compare the health care costs and clinical outcomes of treatment with olanzapine and risperidone in patients with an established history of schizophrenia. The perspective adopted in the economic analysis was that of the German health care system.
Economic study type	Cost-utility analysis.
Study population	The study population comprised a hypothetical cohort of patients currently suffering from an acute episode of schizophrenia, and who were being considered for first-line treatment with a second-generation atypical antipsychotic. The patients were assumed to have a long-term history of relapsing schizophrenia and to have no other concurrent psychotic diagnoses or other significant health issues. In addition, the patients were assumed to have not received any form of previous treatment with atypical antipsychotics.
Setting	The study setting was secondary care. The economic study was carried out in Germany.
Dates to which data relate	The effectiveness data were derived from studies published between 1996 and 2001. The price year was 2002.
Source of effectiveness data	The effectiveness data were derived from a review and synthesis of published data.
Modelling	The model structure was split into two distinct treatment phases. The first part of the model was a decision tree that reflected an initial 3-month period of acute treatment in which the treatment intent was aimed primarily at reducing the current acute symptoms and stabilising the patient. The second part of the model was a Markov model tracking the longer term treatment experience of the patients. This phase was a prolonged longer term preventive treatment aimed at preventing acute relapses.
Outcomes assessed in the review	The outcomes assessed in the review were: the clinical response data, defined by a proportional improvement in the Positive and Negative Symptoms Scale (PANSS); the risk of acute relapse; the suicide risk; and the utility values associated with different health states associated with

	schizophrenia.
Study designs and other criteria for inclusion in the review	The authors reported that data for the model were drawn from pivotal clinical trials of atypical antipsychotics, which were generally based on cohorts of adult patients with schizophrenia who had Brief Psychiatric Rating Scale (BPRS) scores of at least 24.
Sources searched to identify primary studies	Not reported.
Criteria used to ensure the validity of primary studies	Not reported.
Methods used to judge relevance and validity, and for extracting data	Not reported.
Number of primary studies included	Approximately 8 primary studies were included in the review of the literature.
Methods of combining primary studies	The authors did not combine the results of the primary studies. The results from only one study were used to populate an individual model parameter.
Investigation of differences between primary studies	Not reported.
Results of the review	For patients treated with olanzapine, 53.0% achieved an improvement in PANSS scores of at least 30%, 36.8% achieved an improvement of at least 40%, and 21.7% achieved an improvement of at least 50%. For patients treated with risperidone, 43.6% achieved an improvement in PANSS scores of at least 30%, 26.7% achieved an improvement of at least 40%, and 12.1% achieved an improvement of at least 50%. The annual relapse rate during the first year of treatment was 19.7% with olanzapine and 23.4% with risperidone. The annual relapse rate after the first year of treatment was 9.4% with both olanzapine and risperidone. The suicide risk rate was 13.1% at acute episode. The suicide completion rates were set to 23%. The utility weights for the health states were 0.56 for acute symptoms as inpatient, 0.60 for acute symptoms as outpatient, and 0.83 for excellent function as outpatient.
Measure of benefits used in the economic analysis	The health benefit measures used in the economic analysis were the number of quality-adjusted life-years (QALYs) gained. The utility values were derived from a published study (Revicki et al. 1996, see 'Other Publications of Related Interest' below for bibliographic details). The study used a standard gamble approach with clinician assessment.
Direct costs	The direct costs to the health care system were included in the analysis. These included the costs of medications, inpatient hospitalisation, clinic visits (psychiatric, general practitioner, social psychiatric and outpatient), residential home care, residential home care with nursing support, sheltered

	accommodation, and the default costs of a suicide attempt. The resource use data were derived from a clinical focus group that comprised four experts (a health economist and three clinical psychiatrists/psychotherapists) with clinical and health economic experience of treating schizophrenia in Germany. Suicide-related costs were derived from an Italian study, as no data specific to Germany were found. Drug doses were based on recommended levels for Germany and an analysis of typical prescribing in Germany using Mediplus IMS data. The unit costs for drugs were derived from German cost data, while the unit costs for other resource use were derived from German health care system sources. Discounting was not relevant, as the costs were incurred during one year, and was therefore not performed. The price year was 2002.
Indirect Costs	The indirect costs were not included.
Currency	Euros (EUR).
Statistical analysis of costs	The costs were treated as point estimates (i.e. the data were deterministic).
Sensitivity analysis	The authors undertook a series of one-way sensitivity analyses to investigate the stability of the base-case estimates. The authors varied the absolute difference in relapse rates between olanzapine and risperidone from 5% to 20%. They also varied the alternative hospital admission rates for patients during an acute episode of schizophrenia (range: 50 to 100%).
Estimated benefits used in the economic analysis	The number of QALYs gained when using olanzapine over risperidone was 0.06 per 100 patients.
Cost results	The costs of treating 100 patients with risperidone were EUR 3,261,334 during the first year of treatment. The costs of treating 100 patients with olanzapine were EUR 3,226,028 during the first year of treatment.
Synthesis of costs and benefits	The costs and benefits were not combined as olanzapine was found to be both more effective and less costly than risperidone (i.e. it was dominant). The results of the sensitivity analysis showed that varying the absolute difference in relapse rate between 5 and 20% had no effect on the model results as, under all scenarios, olanzapine was still found to be dominant. In addition, olanzapine remained less costly than risperidone unless hospital admission rates dropped to just below 20%.
Authors' conclusions	The analysis suggested that first-line use of olanzapine has potential cost and clinical benefit advantages over first-line risperidone in atypical naive patients with a history of relapsing schizophrenia.
CRD COMMENTARY - Selection of comparators	The authors conducted a head-to-head comparison of two second-generation oral atypical antipsychotics (i.e. risperidone and olanzapine). Second-generation oral atypical antipsychotics have recently been recommended as first-line treatment for newly diagnosed patients with schizophrenia. You should consider if these two treatments are currently being used in your own setting.
Validity of estimate of	The authors did not state that a systematic review of the literature had been

measure of effectiveness	undertaken to identify relevant research and minimise biases. They provided only limited details of the review undertaken. The authors used a single study to inform each individual parameter. In some instances the authors reported the reason for using a particular study over others, for example, the study was the most conservative or had the largest study sample. The authors performed a very limited sensitivity analysis of effectiveness data in that they only varied the annual relapse rates. A more extensive sensitivity analysis would have helped demonstrate the reliability of the results.
Validity of estimate of measure of benefit	The estimation of benefits was modelled using a two-part model. The model consisted of a decision tree and Markov model, both of which were appropriate for the study question. The authors provided adequate details of the structure of the model.
Validity of estimate of costs	All the categories of cost relevant to the perspective adopted were included in the analysis. No major relevant costs appear to have been omitted. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. Resource use was derived from an expert panel based on schizophrenia experts. The authors performed a limited sensitivity analysis on these assumptions, only the hospitalisation rate being varied. The unit costs were derived from published sources. No sensitivity analysis of the unit costs was performed. Discounting was unnecessary since all the costs were incurred during one year. The price year was reported, which will aid future inflation exercises.
Other issues	The authors did not make appropriate comparisons of their findings with those from other studies. The issue of the generalisability to other settings was not addressed. The authors do not appear to have presented their results selectively. However, with such a small difference between the two treatment groups in terms of the benefits and costs, the authors should have performed more a thorough and extensive sensitivity analysis. For instance, they could have undertaken probabilistic sensitivity analyses to examine the overall uncertainty in the model parameters. The authors reported a number of further limitations to their study. First, only direct costs were included; other costs such as impacts on carers and lost productivity were not included. Second, the effectiveness data were derived from clinical trials with tightly defined inclusion criteria, which might limit the generalisability of the results. Finally, the authors assumed that treatment response data could be equally applied in both first- and second-line settings.
Implications of the study	The authors reported that their model could be used to compare a wider set of treatment strategies involving other atypical antipsychotics.
Source of funding	None stated.
Bibliographic detail	Beard A M, Maciver F, Clouth J, Ruther E. A decision model to compare health care costs of olanzapine and risperidone treatment of schizophrenia in Germany. European Journal of Health Economics 2006; 7: 165-172
Other publications of related interest	Because readers are likely to encounter and assess individual publications, NHS EED abstracts reflect the original publication as it is written, as a stand-alone paper. Where NHS EED abstractors are able to identify positively that a publication is significantly linked to or informed by other publications, these will be referenced in the text of the abstract and their bibliographic details

	recorded here for information Revicki DA, Shakespeare A, Kind P. Preferences for schizophrenia-related health states: a comparison of patients, caregivers and psychiatrists. Int Clin Psychopharmacol 1996;11:101-8. Palmer CS, Revicki DA, Genduso LA, et al. A cost-effectiveness clinical decision analysis model for schizophrenia. Am J Manage Care 1998;4:345-55. Alexeyeva I, Mauskopf J, Earnshaw S, et al. Comparing olanzapine and ziprasidone in the treatment of schizophrenia: a case study in modeling. J Med Econ 2001;4:179-92.
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Antipsychotic Agents /economics /therapeutic use; Benzodiazepines /economics /therapeutic use; Decision Support Techniques; Germany; Health Care Costs; Hospitalization /economics; Humans; Quality-Adjusted Life Years; Recurrence; Risperidone /economics /therapeutic use; Schizophrenia /drug therapy /economics /prevention & control; Suicide /prevention & control; Treatment Outcome
Accession number	22006008361
Database entry date	31 March 2007
Record status	This is a critical structured abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Beard 2006: HEED record

N/A – Not identified in search of HEED

Edwards 2005: NHS EED record

Cost effectiveness of long-acting risperidone injection versus alternative antipsychotic agents in patients with schizophrenia in the USA

Edwards N C, Locklear J C, Rupnow M F, Diamond R J

Health technology	The study compared the following treatment options for patients with schizophrenia: long-acting risperidone, oral risperidone (average dose 3.8 mg/day), olanzapine (oral antipsychotic agent), long-acting injectable haloperidol depot (typical antipsychotic agent), and quetiapine, ziprasidone and aripiprazole (oral atypical antipsychotic drugs). Further details of the drugs and specific doses were not reported.
Type of intervention	Treatment.
Hypothesis/study question	The study aimed to compare the various treatment options in terms of their cost-effectiveness. The objective of the study was to update the model of a published study that had compared long-acting risperidone with oral atypical antipsychotic agents (risperidone and olanzapine) and a typical antipsychotic agent (the long-acting injectable haloperidol depot), with current practice patterns and more recent costs, and to expand the analysis by including three more treatment options (quetiapine, ziprasidone and aripiprazole). The last three treatment options seem to have gained great importance and to be commonly used in the authors' setting. The perspective adopted in the economic analysis was that of a health care system.
Economic study type	Cost-effectiveness analysis.
Study population	The target patient population comprised community-dwelling patients with schizophrenia who had previously experienced a relapse necessitating hospitalisation. No further inclusion or exclusion criteria were reported.
Setting	The setting was the community. The economic study was carried out in the USA.
Dates to which data relate	Relevant published literature was accessed electronically in July 2004. Most of the effectiveness data were derived from studies published between 1993 and 2003. Further databases (e.g. the Consumer Health Sciences database) were accessed in 2003. The dates to which unpublished data (derived from various clinical trials) referred were not reported. The cost data were derived from various official sources published between 1992 and 2004. Most medical costs were reported for the price year 2003, while some costs (e.g. medication costs) were reported for the fiscal year 2004.
Source of effectiveness data	The effectiveness data were derived from a review and synthesis of completed studies, augmented with unpublished data from clinical trials and expert opinion where data were not available.
Modelling	A decision analytic model was constructed to evaluate the cost-effectiveness of

	long-acting risperidone for patients with schizophrenia using Microsoft Excel 2002 (Microsoft Corp., Redmond). The time horizon of the model was 1 year. In the model, long-acting risperidone was compared with oral risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole and the long-acting injectable haloperidol depot. The weight of each drug was estimated by its market share in the authors' setting. The authors reported that the structure of the model was based on that of a published study (Glazer and Ereshefsky 1996, see 'Other Publications of Related Interest' below for bibliographic details).
Outcomes assessed in the review	The input parameters used in the model were compliance rates, relapse rates, the frequency of relapse, the duration of relapse, and adverse event rates. Compliance rates for long-acting risperidone, oral risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, haloperidol depot and blended oral atypical (to compare long-acting risperidone with oral atypical antipsychotic drugs overall) were compared. Relapse rates and frequency of relapse (per relapsing patient) distinguished between those that did and did not require hospitalisation with atypical and typical antipsychotic agents. In terms of the adverse event rates, extra pyramidal side effects and weight gain experienced with the drug treatments were compared.
Study designs and other criteria for inclusion in the review	Not reported.
Sources searched to identify primary studies	Primarily, the authors searched PubMed for relevant medical literature. They also searched the Consumer Health Sciences database and unpublished data from clinical trials.
Criteria used to ensure the validity of primary studies	Not reported.
Methods used to judge relevance and validity, and for extracting data	Not reported.
Number of primary studies included	Overall, 19 primary studies provided effectiveness evidence.
Methods of combining primary studies	Compliance rates were adjusted to take the differential compliance of atypical and typical agents, as well as the differential compliance of long-acting injectable versus oral agents, into consideration. The compliance rates for long-acting risperidone were adjusted using modelled data. Relapse rates were adjusted to take the differential efficacy of atypical and typical agents into account.
Investigation of differences between primary studies	The authors do not appear to have investigated differences between the primary studies.
Results of the review	The results of the review were too numerous to report here, thus only the main results are presented. The proportion of patients experiencing a relapse requiring hospitalisation in 1 year was 66% for haloperidol depot, 41% for oral risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole, and 26% for long-acting risperidone. The proportion of patients with an exacerbation not requiring hospitalisation was 60% for haloperidol depot, 37% for oral risperidone, olanzapine, quetiapine,

	ziprasidone and aripiprazole, and 24% for long-acting risperidone. The mean number of days of relapse requiring hospitalisation per patient per year was 28 for haloperidol depot, 18 for oral risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole, and 11 for long-acting risperidone. The mean number of days of exacerbation not requiring hospitalisation was 8 for haloperidol depot, 5 for oral risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole, and 3 for long-acting risperidone.
Methods used to derive estimates of effectiveness	Effectiveness data that were not available in the literature were based on expert opinion. Modified Delphi panel techniques were used to elicit input from clinical experts.
Estimates of effectiveness and key assumptions	The duration of relapse not requiring hospitalisation was 5.0.
Measure of benefits used in the economic analysis	The health benefit measures used were the number of relapses averted per patient per year and the number of relapse days averted per year. These measures were derived from the outcomes.
Direct costs	Adopting the health care system perspective, the direct costs included in the analysis were for inpatient care (hospitalisation, day hospital and emergency room), outpatient care (physician office visit, mental health clinic visit, home health care, social or group therapy meetings, nutritionist) and medications (long-acting risperidone, oral risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole blended oral atypical agent, haloperidol depot and benzodiazepine). The costs were derived from actual published data, while the estimation of the quantities of resources used was based on expert opinion. All unit costs were reported. However, the authors seem to have reported medical costs for the year 2003, while the costs of medication and injection administration, medication utilisation and dose distribution for long-acting risperidone were reported for the year 2004. Since the time horizon of the model was 1 year, discounting was not relevant.
Indirect Costs	The indirect costs were not included in the analysis.
Currency	US dollars ($).
Statistical analysis of costs	The costs were treated deterministically.
Sensitivity analysis	A sensitivity analysis was carried out to test variability in the data. All input parameters of the model were investigated. Although the type of sensitivity analysis was not explicitly stated, the authors seem to have carried out a one-way sensitivity analysis. The authors used 95% confidence intervals (CIs) available in the literature, and ranges based on clinical input where the 95% CI were not available.
Estimated benefits used in the economic analysis	Compared with oral atypical antipsychotic agents, long-acting risperidone resulted in a 15.3% reduction in relapse rate requiring hospitalisation and a 12.9% reduction in relapse rate not requiring hospitalisation. The incremental benefits of long-acting risperidone compared with oral atypical antipsychotic agents were 0.6 relapses averted per patient per year, 6.5 days of relapse requiring hospitalisation saved per patient per year, and 1.7 days of relapse not requiring hospitalisation saved per patient per year.

Cost results	The total treatment costs were reported per patient per year. The total cost was $20,769 for long-acting risperidone, $20,929 for oral risperidone, $22,194 for olanzapine, $21,276 for quetiapine, $21,028 for ziprasidone, $21,837 for aripiprazole, $21,493 for blended oral atypical agent, and $28,992 for haloperidol depot. Using long-acting risperidone rather than an oral atypical antipsychotic agent resulted in $161 of health care savings per patient per year compared with oral risperidone, $259 compared with ziprasidone, $508 compared with quetiapine, $1,068 compared with aripiprazole, and $1,425 compared with olanzapine. Compared with the class of oral atypical antipsychotic agents overall (weighting oral atypical agents by market share), long-acting risperidone resulted in $724 of health care savings per patient per year.
Synthesis of costs and benefits	The costs and benefits were combined using an incremental cost-effectiveness ratio. Long-acting risperidone was found to be dominant, i.e. more effective and less costly than all other treatment options. The sensitivity analysis demonstrated the most influential parameters of the model. If the relapse rate requiring hospitalisation of compliant patients was changed to the upper 95% CI, long-acting risperidone became more costly in comparison with an oral atypical antipsychotic agent or oral risperidone. The model was sensitive when: the hospitalisation relapse rate of partially compliant patients and non-compliant patients was changed to the lower 95% CI; the compliance rate of non-compliant patients was changed to the lower 95% CI; the compliance rates of compliant patients was changed to the upper 95% CI; the frequency of relapse requiring hospitalisation and the frequency of relapse not requiring hospitalisation were changed to the upper 95% CI; and the relapse rate not requiring hospitalisation of compliant patients was changed to the upper 95% CI. The model was also sensitive when the duration of relapse requiring hospitalisation took the minimum value in literature (i.e. 18.2 days). In all the above cases, long-acting risperidone proved to be more costly than oral atypical antipsychotic agents or oral risperidone, and incremental cost-effectiveness ratios were calculated. When all the cost parameters were varied by +/- 25%, the results were only sensitive to the cost of hospitalisation. When the hospitalisation cost was decreased by 10 or 25%, long-acting risperidone became a more costly option than oral risperidone; when it was decreased by 25% long-acting risperidone became more costly than all other treatment options.
Authors' conclusions	The use of long-acting risperidone is predicted to result in better clinical outcomes and lower total health care costs than its comparators (i.e. oral risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole and haloperidol depot). Long-acting risperidone may, therefore, be a cost-saving therapeutic option for patients with schizophrenia.
CRD COMMENTARY - Selection of comparators	The selection of the comparators was explicitly justified. You should decide if

	they represent widely used technologies in your own setting.
Validity of estimate of measure of effectiveness	It appears that a systematic review of the literature was undertaken. The study designs, other inclusion criteria for the review, and possible differences between the primary studies were not investigated. However, the authors conducted an extensive sensitivity analysis to test variability in the data, which enhances the generalisability of the results. Where effectiveness data were not available in the literature, the authors used expert opinion. A Delphi panel of two experts was assembled to derive the estimates of effectiveness, but the authors did not report how the members of the Delphi panel were selected.
Validity of estimate of measure of benefit	The authors used the number of relapses averted per patient per year and the number of relapse days averted per year as the measures of benefit in the economic analysis. Theses outcome measures did not provide a sense of the wider non-health benefits associated with treatment. It would appear that the benefits were not discounted given the short time period of the study analysis.
Validity of estimate of costs	Adopting the health care system perspective it seems that all the relevant categories of costs were included in the analysis. The unit costs were reported, thus enhancing the reproducibility of the results to other settings. However, as already noted, not all costs were reported for the same price year and this factor should be taken into account in any future reflation exercise. Resource use was mainly derived on the basis of expert opinion. Statistical analyses of the resource quantities or costs were not conducted (i.e. the costs were treated deterministically). However, the robustness of the estimates used was investigated in a sensitivity analysis using appropriate ranges. This facilitates the interpretation of the study findings. Discounting was not necessary, as the costs were incurred during less than 2 years.
Other issues	The authors did not compare their findings with those from other studies, so it is not known how far their results agree with other published results. However, this might have been due to the lack of published studies comparing all available treatment options. The structure of the model was straightforward, and the authors felt that it could be easily adapted to other settings to reflect different practice patterns and costs. The authors do not appear to have presented their results selectively. The authors reported a number of limitations to their study. First, the indirect costs were not included in the analysis, although the inclusion of such costs would most probably strengthen the conclusions. Second, research published after July 2004 was not included in the base-case analysis. However, the authors compared the results of the sensitivity analysis with those of some studies published after the time of their PubMed search, and found consistency in their findings. The authors acknowledged that some effectiveness estimates were based on expert opinion and information contained in databases, and not on peer-reviewed published literature, owing to the lack of available studies. On the other hand, they reported that selection bias of the patient population might have affected the results of some peer-reviewed studies on compliance for depot antipsychotic agents.
Implications of the study	The authors did not make any explicit recommendations for changes in policy or practice, or for the need for future research. Their discussion, however, highlighted some areas where more information is needed.
Source of funding	Supported by Janssen Medical Affairs LLC.

Bibliographic detail	Edwards N C, Locklear J C, Rupnow M F, Diamond R J. Cost effectiveness of long-acting risperidone injection versus alternative antipsychotic agents in patients with schizophrenia in the USA. Pharmacoeconomics 2005; 23(Supplement 1): 75-89
Link to Pubmed record	16416763
Other publications of related interest	Glazer WM, Ereshefsky LA. Pharmacoeconomic model of outpatient antipsychotic therapy in "revolving door" schizophrenic patients. J Clin Psychiatry 1996;57:337-45.
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Antipsychotic Agents /administration & dosage /economics /therapeutic use; Cost of Illness; Cost-Benefit Analysis; Decision Trees; Hospitalization /economics /trends; Humans; Injections, Intravenous; Patient Compliance; Research Support, Non-U.S. Gov't; Risperidone /administration & dosage /economics /therapeutic use; Schizophrenia /drug therapy /economics; United States
Accession number	22005008352
Database entry date	31 May 2006
Record status	This is a critical structured abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Edwards 2005: HEED record

Article Reference No	036381
Author	Edwards N C, Locklear J C, Rupnow M F T, Diamond R J
Article Title	Cost effectiveness of long-acting risperidone injection versus alternative antipsychotic agents in patients with schizophrenia in the USA
Journal Name	PharmacoEconomics
Journal Date	2005
Journal Reference	23(suppl 1):75-89
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence and offprints: Natalie Christine Edwards, Health Services Consulting Corporation, 169 Summer Road, Boxborough, MA 01719, USA. E-mail: natalie.edwards@earthlink.net
Cost Base Year	2003
Source Of Article	O
Countries Of Authors	USA
Countries Applicable	USA
Type Of Article	Applied study
Type Of Econ Eval	Cost consequences
Technology Assessed	Pharmaceutical
ATC Codes	N05A
ICD-9 Codes	295
Drug Names	LONG-ACTING RISPERIDONE; ORAL RISPERIDONE; OLANZAPINE; QUETIAPINE; ZIPRASIDONE; ARIPIPRAZOLE; HALOPERIDOL DEPOT
Prob. of Main Clinical Events	Observational data;Other literature review
Quantities of Resources Used	Judgement;Modelling
Prices or Costs of Resources	National Publication;'Ad Hoc' Estimation
Outcomes	Observational data;Other literature review;Modelling
Outcome Measure	Relapse rate
Costs Included	Direct provider/purchaser costs
Sensitivity Tested	Sensitivity tested
Quantitatively Reported	Quantitatively reported
Study Question	This modelling study estimates costs, and effects in terms of relapses, for long acting risperidone injection for patients with schizophrenia in the USA. The intervention is compared to other alternative antipsychotic agents, and parameters for the model are taken from published literature, unpublished data, a consumer

	database, and expert opinion.
Key Results	This study undertakes modelling to estimate costs and effects, in terms of relapses, for long acting risperidone injection for schizophrenia. This is compared to other alternative antipsychotic agents, oral risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole and haloperidol depot. Hospitalisation related relapse was 66 per cent for haloperidol depot, 41 per cent for oral risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole and 26 per cent for long-acting risperidone. None hospitalisation relapse rates were 60 per cent for haloperidol depot, 37 per cent for oral risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole and 24 per cent for long-acting risperidone. Medical cost savings with long-acting risperidone compared with oral risperidone were US$161, compared to olanzapine US$1,425, quetiapine US$508, ziprasidone US$259, aripiprazole US$1,068, and compared to haloperidol depot savings of US$8,224. Some dominance issues came to light during sensitivity analyses, but in general options were supported.
Patient Group	Patients with schizophrenia
Sponsor	Pharmaceutical industry
Keywords	Schizophrenia;Cost Consequences Analysis;Pharmaceutical

Edwards 2008: NHS EED record

One-year clinical and economic consequences of oral atypical antipsychotics in the treatment of schizophrenia

Edwards NC, Pesa J, Meletiche DM, Engelhart L, Thompson AK, Sherr J, Dirani R

CRD summary	The objective was to examine the clinical and economic impact of the oral atypical antipsychotics, aripiprazole, olanzapine, paliperidone extended release, quetiapine, risperidone, and ziprasidone, for the treatment of schizophrenia. The authors concluded that paliperidone extended release had the most favourable clinical and economic outcomes. The study was satisfactorily presented and despite some methodological limitations, the authors' conclusions appear to be valid.
Type of economic evaluation	Cost-effectiveness analysis
Study objective	The objective was to examine the clinical and economic impact of various oral atypical antipsychotics for the treatment of schizophrenia in patients who had suffered an acute exacerbation.
Interventions	The treatments were aripiprazole, olanzapine, paliperidone extended release, quetiapine, risperidone, and ziprasidone.
Location/setting	USA/secondary care.
Methods	Analytical approach: The analysis was based on a decision model that estimated the costs and benefits of the antipsychotics over a one-year time horizon. The authors stated that the analysis was carried out from the perspective of the health care system. Effectiveness data: The key clinical input was the response rate associated with each therapy. These were derived from double-blind, placebo, randomised controlled trials (RCTs), which were identified through a literature review within commonly used electronic databases. No head-to-head trials that included all the medications were found and a common comparator was required. The key details of these trials were reported and they differed in their designs, patients, and length of follow-up. When more than one appropriate RCT was available for a drug, the clinical data were pooled using a weighted average. Other data on discontinuation and adverse events were from a phase I trial. To simplify the model, it was assumed that patients could switch between medications only once per year. Monetary benefit and utility valuations: Not included. Measure of benefit: The summary benefit measure was the number of additional days with no relapse (stable days). Cost data: The economic analysis included the drugs, in-patient services (hospitalisations, day-patient visits, and emergency room visits), and out-patient services (physician visits, mental health clinic visits, social or group therapy visits, nutritionist visits, and other medications). The costs associated with the management of relevant adverse events were also included. The unit costs were from average wholesale prices. The quantities of resources were based on common drug-use data reported in an official database, supplemented with data from a panel of clinical experts. All costs were in US dollars ($) and the price year was 2008. Analysis of uncertainty: Alternative assumptions were considered in a

	deterministic one-way sensitivity analysis. Alternative drug costs were based on Medicare rates and other assumptions were based on published evidence or authors' opinions.
Results	The number of stable days per patient was 346.0 with aripiprazole, 348.7 with olanzapine, 349.1 with paliperidone, 347.1 with quetiapine, 347.7 with risperidone, and 345.4 with ziprasidone. The number of relapses per patient was 2.3 with aripiprazole, 2.0 with olanzapine, 2.0 with paliperidone, 2.2 with quetiapine, 2.0 with risperidone, and 2.4 with ziprasidone. The mean number of days of relapse per patient was 19.0 with aripiprazole, 16.3 with olanzapine, 15.9 with paliperidone, 17.9 with quetiapine, 17.3 with risperidone, and 19.6 with ziprasidone. The total costs per patient were $19,108 with aripiprazole, $18,163 with olanzapine, $16,904 with paliperidone, $18,095 with quetiapine, $17,697 with risperidone, and $19,063 with ziprasidone. Cost-effectiveness ratios were not calculated as paliperidone extended release was dominant, which means it was more effective and less expensive than the comparators. The sensitivity analysis showed that paliperidone remained the cheapest and most effective treatment in all scenarios except two. When the response rate of all comparators was changed to the risperidone response rate and olanzapine had fewer days of relapse than paliperidone, the incremental cost per extra day with no relapse for olanzapine over paliperidone was $1,529. When the price of risperidone was decreased to 50% of the brand price, the incremental cost per extra day with no relapse for risperidone over paliperidone was $4.
Authors' conclusions	The authors concluded that paliperidone extended release had the most favourable clinical and economic outcomes compared with the other oral atypical antipsychotics.
CRD commentary	Interventions: The selection of the comparators was appropriate as they were the available oral atypical antipsychotics in the USA. Effectiveness/benefits: The analysis was based on sources identified through a literature review, the key details of which were reported. RCTs were selected on the basis of characteristics, such as the duration of follow-up and type of clinical outcome. The authors noted that one limitation was the lack of published head-to-head clinical trials, which meant that indirect comparisons were required. This approach is generally limited due to heterogeneity between trials. The use of RCTs was appropriate as they are well designed. Key information on the data sources was given. The benefit measure was disease-specific and might not allow comparisons with the benefits of other health care interventions. Costs: The economic analysis was satisfactorily presented and carried out. The cost categories were consistent with the perspective. The unit costs, data sources, price year, and use of alternative estimates from other payers were reported. The cost estimates were treated deterministically and only a few values were varied in the sensitivity analysis. Analysis and results: The outcomes were clearly presented and were synthesised, when required, in an appropriate incremental analysis. The investigation of uncertainty was restricted to a univariate approach, which identified the most influential model inputs, but did not allow a comprehensive evaluation of the overall uncertainty. It was stated that the analysis was limited by the lack of a direct comparison between medications in the clinical literature

	and future studies were required to overcome this issue. Concluding remarks: The study was satisfactorily presented and, despite some methodological limitations, the authors' conclusions appear to be valid.
Source of funding	Supported by Ortho-McNeil Janssen Scientific Affairs, LLC.
Bibliographic details	Edwards NC, Pesa J, Meletiche DM, Engelhart L, Thompson AK, Sherr J, Dirani R. One-year clinical and economic consequences of oral atypical antipsychotics in the treatment of schizophrenia. Current Medical Research and Opinion 2008; 24(12): 3341-3355
Link to Pubmed record	18954497
URL for original research	http://informahealthcare.com/doi/abs/10.1185/03007990802490512
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Administration, Oral; Antipsychotic Agents /economics /therapeutic use; Female; Health Expenditures; Humans; Male; Medicaid; Medicare; Models, Theoretical; Randomized Controlled Trials as Topic; Schizophrenia /drug therapy /economics; United States; United States Department of Veterans Affairs
Accession number	22009101239
Database entry date	19 May 2010
Record status	This is a critical structured abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Edwards 2008: HEED record

Article Reference No	070197
Author	Edwards N C, Pesa J, Meletiche D M, Engelhart L, Thompson A K, Sherr J, Dirani R
Article Title	One-year clinical and economic consequences of oral atypical antipsychotics in the treatment ofschizophrenia
Journal Name	Current Medical Research and Opinion
Journal Date	2008
Journal Reference	24(12):3341-3355
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence: Natalie C. Edwards, MSc, President, Health Services Consulting Corporation, 169 Summer Road, Boxborough, MA 01719, USA. E-mail: natalie.edwards@earthlink.net
Cost Base Year	2008
Source Of Article	O
Countries Of Authors	USA
Countries Applicable	USA
Type Of Article	Applied study
Type Of Econ Eval	Cost effectiveness analysis
Technology Assessed	Pharmaceutical
ATC Codes	N05A
ICD-9 Codes	295
Drug Names	ARIPIPRAZOLE - Abilify; OLANZAPINE - Zyprexa; PALIPERIDONE ER - Invega; QUETIAPINE - Seroquel; RISPERIDONE - Risperdal; ZIPRASIDONE - Geodon
Prob. of Main Clinical Events	Systematic review and/or meta analysis;Judgement;Modelling
Quantities of Resources Used	Systematic review and/or meta analysis;Judgement;Modelling
Prices or Costs of Resources	National Publication;Local Standard Prices
Outcomes	Systematic review and/or meta analysis;Judgement;Modelling
Outcome Measure	Number of days of relapse, number of stable days, extrapyramidal symptoms, clinically significant weight gain
Costs Included	Hospital costs;Direct provider/purchaser costs
Quantitatively Reported	Quantitatively reported
Study Question	To evaluate the cost-effectiveness of oral atypical antipsychotics (aripiprazole, olanzapine, paliperidone ER, quetiapine, risperidone, and ziprasidone) in the treatment of schizophrenia. The study uses decision analytic modelling with a one-year time horizon and adopts a US healthcare system perspective.

Key Results	The lowest costing treatment over 1-year was paliperidone ER, followed by risperidone, quetiapine, olanzapine, ziprasidone and aripiprazole. Paliperidone ER remained the most effective and least costly treatment throughout all sensitivity analyses except in two instances: (i) when the response rate of all comparators was changed to the risperidone response rate and olanzapine had fewer days of relapse than paliperidone; and (ii) when the price of risperidone was decreased to 50% of brand price it became the least costly product. Overall, the authors conclude that the study showed that paliperidone ER had the most favourable clinical and economic outcomes compared to other oral atypical antipsychotics for patients with schizophrenia, and that the analysis supports the notion that frequent discontinuation of medication is a problem with all oral antipsychotic treatments for schizophrenia.
Patient Group	Hypothetical patients with schizophrenia who have suffered an acute exacerbation of illness.
Sponsor	Pharmaceutical industry
Keywords	Cost Consequences Analysis;Drugs;Schizophrenia;Modelling

Furiak 2009: NHS EED record

N/A – Not identified in search of NHS EED

Furiak 2009: HEED record

Article Reference No	070336
Author	Furiak N M, Ascher-Svanum H, Klein R W, Smolen L J, Lawson A H, Conley R R, Culler S D
Article Title	Cost-effectiveness model comparing olanzapine and other oral atypical antipsychotics in the treatment of schizophrenia in the United States
Journal Name	Cost Effectiveness and Resource Allocation
Journal Date	2009
Journal Reference	7:4
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence: Haya Ascher-Svanum, Eli Lilly and Company, Indianapolis, IN, USA. Email: haya@lilly.com
Cost Base Year	2007
Source Of Article	O
Countries Of Authors	USA
Countries Applicable	USA
Type Of Article	Applied study
Type Of Econ Eval	Cost utility analysis
Technology Assessed	Pharmaceutical
ATC Codes	N05A
ICD-9 Codes	295
Drug Names	OLANZAPINE; RISPERIDONE; QUETIAPINE; ZIPRASIDONE; ARIPIPRAZOLE
Prob. of Main Clinical Events	Other literature review;Judgement;Modelling
Quantities of Resources Used	Other literature review;Judgement;Modelling
Prices or Costs of Resources	National Publication;Local Standard Costs;Judgement
Outcomes	Other literature review;Judgement;Modelling
Values Of Outcomes	Previously Published Values;Judgement
Outcome Measure	QALYs gained, adherence levels, relapse with and without hospitalisation, treatment discontinuation by reason, treatment-emergent adverse events, suicide.
Source Of Data	Incorporated from another study
Costs Included	Hospital costs;Direct provider/purchaser costs
Quantitatively Reported	Quantitatively reported
Abstract	Background: Schizophrenia is often a persistent and costly illness that requires continued treatment with antipsychotics. Differences among antipsychotics on efficacy, safety, tolerability, adherence,

	and cost have cost-effectiveness implications for treating schizophrenia. This study compares the cost-effectiveness of oral olanzapine, oral risperidone (at generic cost, primary comparator), quetiapine, ziprasidone, and aripiprazole in the treatment of patients with schizophrenia from the perspective of third-party payers in the U.S. health care system. Methods: A 1-year microsimulation economic decision model, with quarterly cycles, was developed to simulate the dynamic nature of usual care of schizophrenia patients who switch, continue, discontinue, and restart their medications. The model captures clinical and cost parameters including adherence levels, relapse with and without hospitalization, quality-adjusted life years (QALYs), treatment discontinuation by reason, treatment-emergent adverse events, suicide, health care resource utilization, and direct medical care costs. Published medical literature and a clinical expert panel were used to develop baseline model assumptions. Key model outcomes included mean annual total direct cost per treatment, cost per stable patient, and incremental cost-effectiveness values per QALY gained. Results: The results of the microsimulation model indicated that olanzapine had the lowest mean annual direct health care cost ($8,544) followed by generic risperidone ($9,080). In addition, olanzapine resulted in more QALYs than risperidone (0.733 vs. 0.719). The base case and multiple sensitivity analyses found olanzapine to be the dominant choice in terms of incremental cost-effectiveness per QALY gained. Conclusion: The utilization of olanzapine is predicted in this model to result in better clinical outcomes and lower total direct health care costs compared to generic risperidone, quetiapine, ziprasidone, and aripiprazole. Olanzapine may, therefore, be a cost-effective therapeutic option for patients with schizophrenia.
Study Question	To compares the cost-effectiveness of oral olanzapine, oral risperidone (at generic cost, primary comparator), quetiapine, ziprasidone, and aripiprazole in the treatment of patients with schizophrenia from the perspective of third-party payers in the U.S. health care system. The study uses Markov modelling with a 1 year time horizon.
Key Results	Olanzapine has the lowest mean annual direct health care cost (US$8,544) followed by generic risperidone (US$9,080). Olanzapine also resulted in more QALYs than risperidone (0.733 vs. 0.719 respectively). The results from both the base case analysis and multiple sensitivity analyses indicated that olanzapine is the dominant option in terms of incremental cost per QALY gained. Olanzapine is, therefore, projected to be a cost-effective therapeutic option for patients with schizophrenia in the United States, even with oral risperidone available in generic form and cost. In conclusion, the authors caution that their model simulates real-world treatment processes and provides projections that should be used only to inform decision-making processes from the US health

	care system perspective, and that while their results are consistent with several previous studies, the model will require revision and validation of baseline assumptions when new and additional relevant scientific data become available.
Patient Group	A hypothetical population of 1,000,000 simulated patients with schizophrenia.
Sponsor	Pharmaceutical industry
Keywords	Cost Utility Analysis;Drugs;Modelling;Schizophrenia

Geitona 2008: NHS EED Record

Costs and effects of paliperidone extended release compared with alternative oral antipsychotic agents in patients with schizophrenia in Greece: a cost effectiveness study

Geitona M, Kousoulakou H, Ollandezos M, Athanasakis K, Papanicolaou S, Kyriopoulos I

CRD summary	The objective was to examine the cost-effectiveness of paliperidone extended release in comparison with other prescribed oral treatments for patients with schizophrenia and suffering from acute exacerbations. The authors concluded that paliperidone was more effective and less expensive than other commonly prescribed antipsychotic drugs from the perspective of the Greek National Health System. The study was well conducted and satisfactorily presented. The authors' conclusions appear to be valid.
Type of economic evaluation	Cost-effectiveness analysis
Study objective	The objective was to examine the cost-effectiveness of oral paliperidone extended release in comparison with other prescribed oral treatments for patients with schizophrenia and suffering from acute exacerbations.
Interventions	Oral paliperidone (3mg, 6mg, 9mg, or 12mg per day) extended release was compared against olanzapine 10mg per day, risperidone 6mg per day, quetiapine 750mg per day, ziprasidone 80mg or 160mg per day, and aripiprazole 20mg or 30mg per day.
Location/setting	Greece/secondary care.
Methods	Analytical approach: This economic evaluation was based on a decision tree model with a one-year time horizon. The authors stated that the perspective of the Greek National Health System was taken. Effectiveness data: The clinical inputs for the model were derived from a systematic search of the literature in the PubMed database, which includes MEDLINE. The search and inclusion criteria were described. The search identified randomised controlled trials (RCTs) and the methodological details of these were reported. The criteria used to select the estimates from those found in the literature were reported. There was a lack of head-to-head trials for the comparators and placebo was used as a common comparator. The trial results were adjusted to take into account the different placebo effects. The main clinical estimate was the response rate and this was taken from these trials. Discontinuation and relapse rates and adverse event data came from other studies that were not fully described. Monetary benefit and utility valuations: Not included. Measure of benefit: The summary benefit measure was the annual number of stable days (days with no symptoms). Cost data: The economic analysis included the costs of the drugs, hospitalisations, physician visits, mental health clinic visits, emergency room visits, home care, visits to social or group therapy, and visits to nutritionists. The data on resource consumption were derived from an expert panel of 10 Greek psychiatrists and six health economists, who were selected on the basis of the geographic distribution of the psychiatric units across Greece. The process used to reach a consensus among these experts was described in detail. The unit costs were derived from tariffs reimbursed by the Social Insurance Fund. The drug costs were estimated using their official retail prices and the average daily dose.

	Paliperidone was not marketed in Greece at the time of this study and so the maximum retail price in Europe was used based on the three available doses (3mg, 6mg, and 9mg). All costs were in Euros (EUR) and the price year was not explicitly reported. Analysis of uncertainty: A deterministic one-way sensitivity analysis was undertaken on the most uncertain model inputs, such as those derived from the expert panel, including the frequency and duration of relapses and resource use, due to adverse events, on stable days. An arbitrary range of ±10% was used.
Results	The mean number of stable days was 272.5 with paliperidone, 272.2 with olanzapine, 265.5 with risperidone, 260.7 with quetiapine, 258.6 with ziprasidone, and 260.5 with aripiprazole. The annual cost per patient was EUR 7,030 with paliperidone, EUR 7,034 with olanzapine, EUR 7,082 with risperidone, EUR 8,321 with quetiapine, EUR 7,807 with ziprasidone, and EUR 7,713 with aripiprazole. Paliperidone was the dominant strategy as it was both more effective and less costly than all its comparators. The sensitivity analysis confirmed that the base-case findings were robust and paliperidone remained dominant or very cost-effective compared with the other treatments.
Authors' conclusions	The authors concluded that extended release paliperidone was more effective and less expensive than other commonly prescribed antipsychotic drugs from the perspective of the Greek National Health System. They stated that future research should focus on data collection in clinical practice and comparisons with other countries.
CRD commentary	Interventions: The rationale for the selection of the comparators was clear. The authors compared the commonly used antipsychotic drugs in Greece with the new oral atypical antipsychotic paliperidone extended release. A minimum market share of 4% was required for inclusion. Effectiveness/benefits: The clinical data were based on a systematic review of the literature, which should have ensured the inclusion of all relevant trials. The authors provided extensive detail on the inclusion criteria, and only RCTs were selected. This should ensure the internal validity of the analysis. Due to the lack of direct comparisons between the treatments, placebo was used as a common comparator, which is a valid method. Some details were provided for the RCTs selected. Only the most severe adverse events for each drug were considered and this was acknowledged as a possible limitation of the analysis. The measure of benefit was disease-specific and cannot be compared with the benefits of studies of other diseases. Costs: The economic analysis was well conducted. The categories of costs were consistent with the perspective of the public payer. Extensive information was provided on the unit costs and quantities of resources used. The data sources were clearly presented and the details were reported on the approach used to select the panel of experts. This approach should have ensured that the panel represented the experience within the Greek health care system, but the authors pointed out that it might be biased by personal experience with individual cases. The procedure used to reach a consensus among experts was reported. These features enhance the transparency of the economic analysis. The provision of the price year would have been helpful for reflation exercises for other time periods. The authors noted that the use of the highest European price for paliperidone biased the economic results against the drug, which made

	their findings conservative. Analysis and results: The authors provided extensive information on the decision model, and explicitly reported the structure, pathways, and assumptions. The approach used to analyse the costs and benefits was appropriate and a synthesis was not required because one treatment dominated the others. A more comprehensive investigation of the uncertainty would have been more appropriate, but the findings appear to have been robust to variations in the assumptions. The authors noted some methodological limitations of their study, such as the use of a one-year time frame, which was due to the lack of reliable long-term evidence. Other potential limitations have already been reported. Concluding remarks: The study was well conducted and satisfactorily presented. The authors' conclusions appear to be valid.
Source of funding	Funding received from Janssen-Cilag Pharmaceutical SACI.
Bibliographic details	Geitona M, Kousoulakou H, Ollandezos M, Athanasakis K, Papanicolaou S, Kyriopoulos I. Costs and effects of paliperidone extended release compared with alternative oral antipsychotic agents in patients with schizophrenia in Greece: a cost effectiveness study. Annals of General Psychiatry 2008; 7:16
Link to Pubmed record	18755025
URL for original research	http://www.annals-general-psychiatry.com/content/pdf/1744-859X-7-16.pdf
URL for additional data	http://www.annals-general-psychiatry.com/content/pdf/1744-859X-8-15.pdf
Other publications of related interest	Kane J, Canas F, Kramer M, Ford L, Gassmann-Mayer C, Lim P, Eerdekens M. Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. Schizophrenia Research 2007; 90: 147-161. Marder SR, Kramer M, Ford L, Eerdekens E, Lim P, Eerdekens M, Lowy A. Efficacy and safety of paliperidone extended-release tablets: results of a 6-week, randomized, placebo-controlled study. Biological Psychiatry 2007; 62: 1363-1370. Owen RT. Extended-release paliperidone: efficacy, safety and tolerability profile of a new atypical antipsychotic. Drugs Today 2007; 43: 249-258. Almond S, O'Donnell O. Cost analysis of the treatment of schizophrenia in the UK. A comparison of olanzapine and haloperidol. Pharmacoeconomics 1998; 13: 575-588.
Subject index terms status	Subject indexing assigned by CRD
Subject index terms	Antipsychotic Agents; Cost-Benefit Analysis; Greece; Humans; Schizophrenia
Accession number	22008101985
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Record status	This is a critical structured abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Geitona 2008: HEED Record

Article Reference No	074017
Author	Geitona M, Kousoulakou H, Ollandezos M, Athanasakis K, Papanicolaou S, Kyriopoulos I
Article Title	Costs and effects of paliperidone extended release compared with alternative oral antipsychotic agents in patients with schizophrenia in Greece: A cost effectiveness
Journal Name	Annals of General Psychiatry
Journal Date	2008
Journal Reference	7:16
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence: Sotiria Papanicolaou, Janssen-Cilag Pharmaceutical SACI, Eirinis Avenue 56, 15121 Pefki, Athens, Greece. E-mail: spapanic@jacgr.jnj.com
Source Of Article	O
Countries Of Authors	Greece
Countries Applicable	Greece
Type Of Article	Applied study
Type Of Econ Eval	Cost effectiveness analysis
Technology Assessed	Pharmaceutical
ATC Codes	N05A
ICD-9 Codes	295
Drug Names	RISPERIDONE; OLANZAPINE; QUETIAPINE; ZIPRASIDONE; ARIPIPRAZOLE; PALIPERIDONE
Prob. of Main Clinical Events	Observational data;Other literature review
Quantities of Resources Used	Judgement;Modelling
Prices or Costs of Resources	Local Standard Costs
Outcomes	Observational data;Other literature review;Modelling
Outcome Measure	Number of stable days (no symptoms)
Costs Included	Direct provider/purchaser costs
Sensitivity Tested	Sensitivity tested
Quantitatively Reported	Quantitatively reported
Abstract	Background: To compare the costs and effects of paliperidone extended release (ER), a new pharmaceutical treatment for the management of schizophrenia, with the most frequently prescribed oral treatments in Greece (namely risperidone, olanzapine, quetiapine, aripiprazole and ziprasidone) over a 1-year time period. Methods: A decision tree was developed and tailored to the specific

	circumstances of the Greek healthcare system. Therapeutic effectiveness was defined as the annual number of stable days and the clinical data was collected from international clinical trials and published sources. The study population was patients who suffer from schizophrenia with acute exacerbation. During a consensus panel of 10 psychiatrists and 6 health economists, data were collected on the clinical practice and medical resource utilisation. Unit costs were derived from public sources and official reimbursement tariffs. For the comparators official retail prices were used. Since a price had not yet been granted for paliperidone ER at the time of the study, the conservative assumption of including the average of the highest targeted European prices was used, overestimating the price of paliperidone ER in Greece. The study was conducted from the perspective of the National Healthcare System. Results: The data indicate that paliperidone ER might offer an increased number of stable days (272.5 compared to 272.2 for olanzapine, 265.5 f risperidone, 260.7 for quetiapine, 260.5 for ziprasidone and 258.6 for aripiprazole) with a lower cost compared to the other therapies examined (Euros 7,030 compared to Euros 7,034 for olanzapine, Euros 7,082 for risperidone, Euros 8,321 for quetiapine, Euros 7,713 for ziprasidone and Euros 7,807 for aripiprazole). During the sensitivity analysis, a +/- 10% change in the duration and frequency of relapses and the economic parameters did not lead to significant changes in the results. Conclusion: Treatment with paliperidone ER can lead to lower total cost and higher number of stable days in most of the cases examined. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0) which permits unrestricted use, distribution in any medium, provided the original work is properly cited
Study Question	The authors of the study aimed to compare the cost effectiveness of paliperidone extended release (ER) with the alternative frequently prescribed (> or = 4% market share) oral antipsychotic treatments risperidone, olanzapine, quetiapine, aripiprazole and ziprasidone available in Greece. The study was a cost effectiveness analysis based on a decision tree model with branches for each of the 6 aforementioned treatments over a 1 year period where patients could either discontinue, fail to respond at 6 weeks or respond and continue treatment to 1 year. Patients who discontinued could either switch to another oral atypical or discontinue and relapse (with a probability of requiring hospitalization). Patients continuing treatment to 1 year either remained stable or relapsed (with a probability of requiring hospitalization). Effectiveness was measured by the number of stable days (symptom free days). The analysis was carried out under the perspective of the Greek National Health System (NHS)
Key Results	The analysis suggested that use of paliperidone extended release

	(ER) incurred a lower cost (Euros 7,030) compared to the alternative oral antipsychotic treatments risperidone (Euros 7,082, incremental cost Euros 52), olanzapine (Euros 7,034, incremental cost Euros 4), quetiapine (Euros 8,321, incremental cost Euros 1,291), aripiprazole (Euros 7,807, incremental cost Euros 777) and ziprasidone (Euros 7,713, incremental cost Euros683). The analysis also suggested that the effectiveness of paliperidone ER in terms of number of stable days (272.5 days) was higher than for the alternative treatments risperidone (265.5 days, incremental effectiveness -7.0 days) olanzapine (272.2 days, incremental effectiveness -0.3 days), quetiapine (260.7 days, incremental effectiveness -11.8 days), aripiprazole (258.6 days, incremental effectiveness -13.9 days) and ziprasidone (260.5 days, incremental effectiveness -12.0 days). Therefore paliperidone ER appeared to be the dominant treatment for schizophrenia. The results of the analysis appeared robust to increases/decreases of 10% in the duration and frequency of relapses and the economic parameters. The authors concluded that paliperidone ER resulted in better clinical outcomes and lower total direct healthcare costs than the alternative oral antipsychotic treatments.
Patient Group	Patients who suffer from schizophrenia with acute exacerbation
Sponsor	Pharmaceutical industry
Keywords	Schizophrenia;Cost Effectiveness Analysis (CEA);Decision Analysis;Pharmaceutical

Jerrell 2009: NHS EED record

N/A – Not identified in search of NHS EED

Jerrell 2009: HEED record

Article Reference No	077089
Author	Jerrell J M, McIntyre R S
Article Title	Health-care costs of pediatric clients developing adverse events during treatment withantipsychotics
Journal Name	Value in Health
Journal Date	2009
Journal Reference	12(5):716-722
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence: Jeanette M. Jerrell, Department of Neuropsychiatry and Behavioral Science, University of South Carolina School of Medicine, 3555 Harden Street Ext., CEB 301, Columbia, SC 29203, USA. E-mail: Jeanette.Jerrell@uscmed.sc.edu
First Year Cost Data	1996
Last Year Cost Data	2005
Source Of Article	O
Countries Of Authors	USA, Canada
Countries Applicable	USA
Type Of Article	Applied study
Type Of Econ Eval	Cost analysis
Technology Assessed	Pharmaceutical
ATC Codes	N05A
ICD-9 Codes	295; 296; 297; 298; 299; 312; 313; V40
Drug Names	OLANZAPINE; QUETIAPINE; RISPERIDONE; HALOPERIDOL; ARIPIPRAZOLE; ZIPRASIDONE
Quantities of Resources Used	Observational data;Modelling
Prices or Costs of Resources	Specific Estimates;National Publication
Costs Included	Direct provider/purchaser costs
Study Question	Extant clinical trial studies and case reports indicate that the use of conventional antipsychotics and second-generation antipsychotics (SGAs) in children is associated with higher rates of adverse events. Therefore, the aim of this study was to examine the differences over time in health care costs associated with incident adverse events in children and adolescents treated with antipsychotic agents compared to an untreated control sample. Method: In order to do this, a retrospective cohort design evaluating South Carolina's Medicaid medical and pharmacy claims between January 1996 and December 2005 was employed for 4,140 children and adolescents prescribed antipsychotic medications, and a random sample of 4,500 children not treated with psychotropic medications.
Key Results	Patients with the focal adverse medical conditions incurred

	significantly higher total care costs (34% higher, on average, over 8-9 years) compared with those without these conditions ($F = 710.08$; $p < 0.0001$) or to children not treated with psychotropic medications ($F = 2855.54$; $p < 0.0001$). Patients with incident adverse events associated with antipsychotic treatment had significantly higher rates/time under Medicaid coverage of outpatient, emergency, and inpatient services utilisation than the control sample patients, controlling for pre-existing conditions, receipt of multiple psychotropic medications, and individual risk factor differences for males, adolescents, and non-African Americans. Based on these findings, the authors conclude that the development of adverse medical conditions related to antipsychotic medication use in children and adolescents is significantly associated with higher total costs of health care and to utilisation of outpatient, emergency, and inpatient services over time.
Patient Group	4,140 children and adolescents (aged 17 and under; mean age 10.4 yrs; 68.2% male) treated with antipsychotic agents (aripiprazole, ziprasidone, quetiapine, risperidone, olanzapine, or haloperidol) compared to an untreated control sample of 4,500 children and adolescents (mean age, 7.3 yrs). Data were taken from a retrospective cohort in South Carolina's Medicaid medical and pharmacy claims between January 1996 and December 2005. Patients in the treated group had the following conditions: schizophrenia; major affective disorders; other psychotic disorders; attention deficit/hyperactivity disorder; and conduct/oppositional deficit disorder.
Sponsor	Government/publicly funded policy making body
Keywords	Cost Analysis;Mental Illness - Pharmaco Therapy;Adverse Events;Adolescent Services;Pediatrics;Child

Kongsakon 2005: NHS EED record

Cost analysis of the treatment of schizophrenia in Thailand: a simulation model comparing olanzapine, risperidone, quetiapine, ziprasidone and haloperidol

Kongsakon R, Leelahanaj T, Price N, Birinyi-Strachan L, Davey P

Health technology	Several medications for schizophrenia were examined. The four atypical antipsychotics studied were olanzapine (OLZ), risperidone (RISP), quetiapine (QUET) and ziprasidone (ZIP), and the one typical antipsychotic was haloperidol (HAL). All medications were given at the daily defined dose: HAL 8 mg, QUET 400 mg, ZIP 80 mg, RISP 5 mg and OLZ 10 mg.
Type of intervention	Treatment.
Hypothesis/study question	The objective of the study was to assess the cost-effectiveness of the five medication options for the treatment of schizophrenia in Thailand. The authors stated that atypical antipsychotic drugs are used to alleviate the positive symptoms of schizophrenia and studies have shown that they are as effective as typical antipsychotics. They also alleviate negative and depressive symptoms and cause fewer extrapyramidal side-effects than typical antipsychotics. However, their cost is higher in comparison with conventional antipsychotics. Thus, a pharmacoeconomic evaluation is required to support their use in clinical practice. A societal perspective was adopted in the study.
Economic study type	Cost-effectiveness analysis.
Study population	The study population comprised a hypothetical cohort of patients with schizophrenia.
Setting	The setting appears to have been secondary care. The economic study was carried out in Thailand.
Dates to which data relate	The effectiveness data and some resource use data were derived from studies published between 1991 and 2003. A unique price year was not reported.
Source of effectiveness data	The effectiveness evidence was derived from a synthesis of published studies.
Modelling	The authors stated that a model was used to assess the costs of the five alternative treatments for schizophrenia over a 12-month time horizon. However, details of the model were not reported.
Outcomes assessed in the review	The outcomes estimated from the literature were indicators of efficacy and safety for the medications examined in the study. These included anticholinergic use, dropouts (for any reason, for adverse events, or for lack of efficacy), and changes in the Positive and Negative Syndrome Scale (PNSS) and the Brief Psychiatric Rating Scale (BPRS).
Study designs and other criteria for inclusion in the review	A review of the literature was undertaken to identify primary studies providing data on the efficacy of treatment and tolerability. The design of the primary studies was not described in detail, but most of the studies appear to have been randomised clinical trials.
Sources searched to identify	EMBASE (from 1988 to week 42, 2003), MEDLINE (from 1966 to October

primary studies	week 2, 2003) and NHS EED were searched.
Criteria used to ensure the validity of primary studies	Not reported.
Methods used to judge relevance and validity, and for extracting data	Not reported.
Number of primary studies included	Of the 1,175 publications found from the literature, only 31 studies were included in the analysis.
Methods of combining primary studies	The method used to combine the primary studies was not explicitly stated, but weighted mean differences in efficacy between medications were calculated. The difference in tolerability and efficacy between OLZ and RISP and between OLZ and HAL were based on direct comparisons (head-to-head trials), while the difference in tolerability and efficacy between OLZ and QUET and between OLZ and ZIP were based on indirect comparisons (with HAL as the common comparator).
Investigation of differences between primary studies	Not reported.
Results of the review	Only statistically significant results will be reported here. In the short-term, the risk difference in anticholinergic use was -0.06 (95% confidence interval, CI: -0.12 to -0.01; p=0.02) in favour of OLZ compared with RISP, -0.33 (95% CI: -0.37 to -0.30; p<0.00001) in favour of OLZ compared with HAL, and -0.21 (95% CI: -0.31 to -0.12; p<0.001) in favour of RISP compared with HAL. In the short-term, the risk difference in dropouts for any reason was -0.14 (95% CI: -0.22 to -0.05; p=0.002) in favour of OLZ compared with HAL, -0.06 (95% CI: -0.10 to -0.02; p=0.002) in favour of RISP compared with HAL, and -0.1 (95% CI: -0.20 to -0.00; p=0.049) in favour of OLZ compared with QUET via HAL. In the short-term, the risk difference in dropouts due to adverse events was -0.03 (95% CI: -0.05 to -0.01; p=0.003) in favour of OLZ compared with HAL. In the short-term, the risk difference in dropouts due to lack of efficacy was -0.09 (95% CI: -0.12 to - 0.06; p<0.00001) in favour of OLZ compared with HAL. In the long-term, the risk difference in anticholinergic use was -0.15 (95% CI: -0.23 to -0.07; p=0.003) in favour of OLZ compared with RISP, -0.51 (95% CI: -0.83 to -0.19; p=0.002) in favour of OLZ compared with HAL, -0.50 (95% CI: -0.93 to -0.07; p=0.023) in favour of OLZ compared with QUET via HAL, and -0.41 (95% CI: -0.75 to -0.07; p=0.019) in favour of OLZ compared with ZIP via HAL. In the long-term, the risk difference in dropouts due to any reason was -0.12 (95% CI: -0.22 to -0.03; p=0.008) in favour of OLZ compared with RIS, and -0.20 (95% CI: -0.34 to -0.07; p=0.004) in favour of OLZ compared with HAL. In the long-term, the risk difference in dropouts due to lack of efficacy was -0.10 (95% CI: -0.19 to -0.01; p=0.03) in favour of OLZ compared with HAL. Statistically significant results in favour of OLZ were also observed in terms of both short- and long-term efficacy variables. OLZ showed significantly better

	results in: the PANSS total change, PANSS negative change and BPRS total change in comparison with RISP in the long term; all efficacy measures compared with HAL, both in the short- and long-term period; the PANSS total change and BPRS total change compared with QUET in the short term; and the PANSS total change compared with ZIP in the short term.
Measure of benefits used in the economic analysis	The health outcomes were left disaggregated and no summary benefit measure was used in the economic study. In effect, a cost-consequences analysis was carried out.
Direct costs	The analysis of the direct costs appears to have been carried out from the perspective of the health care system. The direct costs included in the analysis were antipsychotics, anticholinergics, hospitalisations and relapse. The unit costs were presented separately from the quantities of resources used. Resource consumption was based on daily defined doses for drugs (with the exception of RISP), a published source for hospitalisations, and authors' assumptions for relapses. The sources used to derive the costs were not reported, with the exception of hospital stay, which was derived from the Ministry of Public Health in Thailand. Discounting was not relevant since the costs were incurred during 12 months. A unique price year was not explicitly reported.
Indirect Costs	The indirect costs (i.e. productivity losses due to unemployment and suicide gestures or attempts) were included in the analysis. The unit costs were reported separately from the quantities of resources used. Resource use was derived from published data and authors' assumptions. The costs were derived using published sources and were based on monthly earnings in Thailand, after taking into account the low employment rate among schizophrenic patients. As in the analysis of the direct costs, discounting was not relevant and the price year was not reported.
Currency	Thailand bath (THB).
Statistical analysis of costs	The costs appear to have been treated deterministically.
Sensitivity analysis	Sensitivity analyses were not performed.
Estimated benefits used in the economic analysis	See the ‚Effectiveness Results- section.
Cost results	Annual medication costs were THB 70,715 with OLZ, THB 43,800 with RISP, THB 5,733 with HAL, THB 81,760 with QUET, and THB 49,458 with ZIP. Other costs (including hospitalisations, other medications, productivity and suicide costs) were THB 32,477 with OLZ, THB 60,694 with RISP, THB 80,156 with HAL, THB 64,738 with QUET, and THB 68,784 with ZIP. The total annual costs were THB 103,225 with OLZ, THB 104,564 with RISP, THB 86,004 with HAL, THB 146,526 with QUET, and THB 118,314 with ZIP.
Synthesis of costs and	A synthesis of the costs and benefits was not relevant as a cost-consequences

benefits	analysis was carried out.
Authors' conclusions	Olanzapine (OLZ) was a dominant treatment for schizophrenia in Thailand in comparison with risperidone (RISP), quetiapine (QUET) and ziprasidone (ZIP), and a cost-effective treatment in comparison with haloperidol (HAL).
CRD COMMENTARY - Selection of comparators	The selection of the comparators appears to have been appropriate for the objective of the analysis. Further, the dosages of each drug were reported. You should decide whether they are valid comparators in your own setting.
Validity of estimate of measure of effectiveness	The effectiveness data were estimated from published studies. A systematic review of the literature was undertaken to identify primary studies. Some information on the search methods (source and key words) was reported, but other details on the methods and conduct of the review were not given. Little information on the design and other characteristics of the primary studies was provided, thus it was not possible to assess the validity of the primary estimates. The comparisons between OLZ and RISP and between OLZ and HAL were based on head-to-head trials, whereas those between OLZ and QUET and OLZ and RISP were based on indirect comparisons (with HAL as common comparator). However, the issue of heterogeneity among the primary studies was not addressed. This represents a limitation of the study, in particular for those comparisons that were not based on head-to-head trials. Moreover, the approach used to combine the primary estimates was not described. The issue of variability in the data was addressed in the sensitivity analysis.
Validity of estimate of measure of benefit	No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).
Validity of estimate of costs	The analysis of the costs included all relevant costs since both the direct and indirect costs were considered. The unit costs were presented separately from the quantities of resources used, which will help in replicating the study in other settings. The source of resource use was clearly reported for all items, whereas for most items the source of the unit costs was not given. The cost estimates were specific to the study setting and the impact of using alternative cost estimates was not investigated. Statistical tests were not carried out and the price year was not reported, which will hinder reflation exercises in other time periods.
Other issues	The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. No sensitivity analyses were carried out, which limits the external validity of the study. The analysis referred to patients with schizophrenia and this was reflected in the authors' conclusions. The authors noted that the cost analysis was a strength of their study. The main limitation of the study was related to the effectiveness analysis and the lack of head-to-head trials for some comparisons. In addition, no cost-effectiveness ratio was provided for the comparison between OLZ and HAL.
Implications of the study	The study results supported the use of OLZ for the treatment of schizophrenia.
Source of funding	None stated.
Bibliographic detail	Kongsakon R, Leelahanaj T, Price N, Birinyi-Strachan L, Davey P. Cost

	analysis of the treatment of schizophrenia in Thailand: a simulation model comparing olanzapine, risperidone, quetiapine, ziprasidone and haloperidol. Journal of the Medical Association of Thailand 2005; 88(9): 1267-1277
Link to Pubmed record	16536115
Other publications of related interest	Kongsakon R, Roungkarnjanaset S. Olanzapine versus Haloperidol in the treatment of refractory schizophrenia: a cost-effectiveness analysis. J Psychiatr Assoc Thailand 2000;45:71-85. Lieberman JA, Tollefson G, Tohen M, Green A. Comparative efficacy and safety of conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. Am J Psych 2003;160:1369. Tollefson GD, Beasley CM, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psych 1997;154:457-65.
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Antipsychotic Agents /classification /economics /therapeutic use; Benzodiazepines /economics /therapeutic use; Comparative Study; Computer Simulation; Cost of Illness; Cost-Benefit Analysis; Dibenzothiazepines /economics /therapeutic use; Drug Costs; Haloperidol /economics /therapeutic use; Health Care Costs; Humans; Models, Econometric; Piperazines /economics /therapeutic use; Risperidone /economics /therapeutic use; Schizophrenia /drug therapy /economics; Thailand; Thiazoles /economics /therapeutic use; Treatment Outcome
Accession number	22006000284
Database entry date	30 June 2006
Record status	This is a critical structured abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Kongsakon 2005: HEED record

Article Reference No	039441
Author	Kongsakon R, Leelahanaj T, Price N, Birinyi-Strachan L, Davey P
Article Title	Cost analysis for the treatment of schizophrenia in Thailand: a simulation model comparing olanzapine, risperidone, quetiapine, ziprasidone and haloperidol
Journal Name	Journal of the Medical Association of Thailand
Journal Date	2005
Journal Reference	88(9):1267-1277
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence: Dr Ronnachai Kongsakon, Department of Psychiatry, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand. E-mail: rarks@mahidol.com
Source Of Article	O
Countries Of Authors	Thailand, Australia
Countries Applicable	Thailand
Type Of Article	Review of applied studies
Type Of Econ Eval	Cost analysis
Technology Assessed	Pharmaceutical
ATC Codes	N05A
ICD-9 Codes	295
Drug Names	OLANZAPINE; RISPERIDONE; QUETIAPINE; ZIPRASIDONE; HALOPERIDOL
Quantities of Resources Used	Observational data
Prices or Costs of Resources	'Ad Hoc' Estimation
Costs Included	Hospital costs;Direct provider/purchaser costs
Study Question	The purpose of this study was to compare the annual costs of treating schizophrenia with four atypical antipsychotics, namely, olanzapine, risperidone, quetiapine and ziprasidone and one typical antipsychotic, haloperidol, in Thailand using a cost analysis model.
Key Results	The purpose of this study was to compare the annual costs of treating schizophrenia with four atypical antipsychotics, namely, olanzapine, risperidone, quetiapine and ziprasidone and one typical antipsychotic, haloperidol, in Thailand using a cost analysis model. The authors carried an international literature review that resulted in 1175 publications out of which 31 satisfied the objectives of the study. Local unit costs associated with olanzapine, risperidone, quetiapine and ziprasidone, expressed in Thai baht (THB) were calculated over a period of 12-months. The analysis included all direct and indirect healthcare cots including those associated with loss of productivity .The total cost from the cost analysis are as

	follows: haloperidol gives the lowest annual cost of THB 86,004, within the atypical antipsychotics, olanzapine produces an annual cost of THB 103,225 compared to THB 104,564 with risperidone and THB 118,314 with ziprazidone. The cost ranges up to THB 146,526 for quetiapine therapy. The authors' concluded that treatment with olanzapine appears to be more cost-effective than that with the other atypical anti psychotics in Thai schizophrenic patients. Keywords: Cost analysis, Schizophrenia, Atypical antipsychotics, Olanzapine, Risperidol, Ziprasidone, Quetiapine, Haloperidol
Patient Group	Patients with schizophrenia in Thailand
Keywords	Cost Analysis;Schizophrenia;Pharmaceutical

McIntyre 2010: NHS EED record

Comparison of the metabolic and economic consequences of long-term treatment of schizophrenia using ziprasidone, olanzapine, quetiapine and risperidone in Canada: a cost-effectiveness analysis

McIntyre RS, Cragin L, Sorensen S, Naci H, Baker T, Roussy JP

Record status	This is an economic evaluation that meets the criteria for inclusion on NHS EED. If you would like us to consider prioritising the writing of a critical abstract for this economic evaluation please e-mail: CRD-NHSEED@york.ac.uk quoting the Accession Number of this record. Please note that priority is given to fast track requests from the UK National Health Service.
Bibliographic detail	McIntyre RS, Cragin L, Sorensen S, Naci H, Baker T, Roussy JP. Comparison of the metabolic and economic consequences of long-term treatment of schizophrenia using ziprasidone, olanzapine, quetiapine and risperidone in Canada: a cost-effectiveness analysis. Journal of Evaluation in Clinical Practice 2010; 16 (4) : 744-755
Link to Pubmed record	20545800
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Adult; Antipsychotic Agents /adverse effects /economics /metabolism /pharmacology; Canada; Cost-Benefit Analysis; Female; Humans; Long-Term Care; Male; Markov Chains; Quality of Life; Schizophrenia /drug therapy
Accession number	22010001339
Database entry date	22 December 2010

McIntyre 2010: HEED record

Article Reference No	075629
Author	McIntyre R S, Cragin L, Sorensen S, Naci H, Baker T, Roussy J-P
Article Title	Comparison of the metabolic and economic consequences of long-term treatment of schizophreniausing ziprasidone, olanzapine, quetiapine and risperidone in Canada: a cost-effectiveness analysis
Journal Name	Journal of Evaluation in Clinical Practice
Journal Date	2010
Journal Reference	6(4):744û755
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence: Jean-Pascal Roussy, Pfizer Canada Inc., Kirkland, Quebec H9J 2M5, Canada. E-mail: jean-pascal.roussy@pfizer.com
Source Of Article	O
Countries Of Authors	Canada, USA
Countries Applicable	Canada
Type Of Article	Applied study
Type Of Econ Eval	Cost utility analysis
Technology Assessed	Pharmaceutical
ATC Codes	N05A
ICD-9 Codes	295; 250; 410; 413; 436
Drug Names	ZIPRASIDONE; OLANZAPINE; QUETIAPINE; RISPERIDONE
Prob. of Main Clinical Events	Observational data;Other literature review
Quantities of Resources Used	Judgement;Modelling
Prices or Costs of Resources	'Ad Hoc' Estimation
Outcomes	Observational data;Other literature review;Modelling
Values Of Outcomes	Previously Published Values
Outcome Measure	Quality-adjusted life years (QALYs) gained
Source Of Data	Patients in study
Costs Included	Hospital costs;Direct provider/purchaser costs
Costs Discounted	5%
Benefits Discounted	5%
Sensitivity Tested	Sensitivity tested
Quantitatively Reported	Quantitatively reported
Abstract	Rationale, aims and objectives: Second-generation antipsychotic agents have varying propensities to cause weight gain, elevated lipid levels and associated long-term complications. This study evaluates the cost-effectiveness of four second-generation antipsychotic agents used in Canada for the treatment of schizophrenia

	(ziprasidone, olanzapine, quetiapine, risperidone) with a focus on their long-term metabolic consequences. Method: Using data from the Clinical Antipsychotic Trials of Intervention Effectiveness Study, a semi-Markov model was developed to predict the incidence and associated costs of type 2 diabetes, cardiovascular complications (e.g. angina, myocardial infarction, stroke, cardiovascular disease death), and acute psychiatric hospitalizations in patients with chronic schizophrenia treated over 5 years. Incremental costs per quality-adjusted life year (QALY) gained were calculated from the perspective of the Canadian provincial ministries of health. Scenario and probabilistic sensitivity analyses were performed. Results: The total average cost of treatment with ziprasidone was $25 301 versus $28 563 with olanzapine, $26 233 with quetiapine and $21 831 with risperidone. Ziprasidone had the lowest predicted number of type 2 diabetes cases and cardiovascular disease events, and the highest QALY gains. Patients receiving quetiapine had the highest predicted number of hospitalizations. Ziprasidone was less costly and resulted in more QALYs compared with olanzapine and quetiapine. Compared with risperidone, ziprasidone was more costly and had higher QALYs, with an incremental cost per QALY gained of $218 060. Conclusion: Compared with olanzapine and quetiapine, ziprasidone produced savings to the health care system. Although ziprasidone generated incremental expenditures versus risperidone, it resulted in more QALYs. Based on this analysis, ziprasidone treatment possesses cost and therapeutic advantages compared with olanzapine and quetiapine. Reproduced by kind permission of Blackwell Science Limited
Study Question	The objective of this study was to assess the predicted incidence and associated costs of developing type 2 diabetes, cardiovascular complications (i.e., angina, myocardial infarction (MI), stroke, cardiac death) and acute psychiatric relapses requiring hospitalization, because of prolonged treatment with second-generation antipsychotics in patients with chronic schizophrenia in Canada. In addition, the study examined the cost-effectiveness of ziprasidone relative to olanzapine, quetiapine and risperidone. The analysis was conducted from the perspective of the Canadian provincial ministries of health
Key Results	The total costs incurred by a patient with schizophrenia from the Canadian provincial health care perspective was estimated at Can$25,301 for patients receiving ziprasidone, Can$28,563 for patients receiving olanzapine, Can$26,233 for patients receiving quetiapine and Can$21,831 for patients treated with risperidone. The predicted number of QALYs gained over 5 years also varied by second-generation antipsychotic received. While an estimated 3.041 quality adjusted life years (QALYs) per patient were gained in patients receiving ziprasidone, 2.982 were accumulated in the olanzapine group, 3.022 with quetiapine and 3.025 with risperidone.

	Patients receiving quetiapine had the highest predicted number of hospitalizations. Ziprasidone was less costly and resulted in more QALYs compared with olanzapine and quetiapine. Compared with risperidone, ziprasidone was more costly and had higher QALYs, with an incremental cost per QALY gained of Can$218,060. The authors concluded that compared with olanzapine and quetiapine, ziprasidone produced savings to the health care system. Although ziprasidone generated incremental expenditures versus risperidone, it resulted in more QALYs. Based on this analysis, ziprasidone treatment possesses cost and therapeutic advantages compared with olanzapine and quetiapine
Patient Group	A hypothetical Canadian cohort of 10,000 adult patients (= or > 18 years of age) with recurrent or chronic schizophrenia including partially remitted outpatients as well as inpatients experiencing exacerbation of illness. Individuals with medical or psychiatric co-morbidities and those who require concomitant medications were also included
Sponsor	Pharmaceutical industry
Keywords	Cost Utility Analysis;QALYs;Quality Adjusted Life Years;Pharmaceutical;Schizophrenia;Angina;Myocardial Infarction;Stroke;Cardiovascular Disease

Mortimer 2003: NHS EED record

Impact of side-effects of atypical antipsychotics on non-compliance, relapse and cost
Mortimer A, Williams P, Meddis D

Health technology	The use of atypical antipsychotics in schizophrenia. Olanzapine, risperidone and ziprasidone were compared with quetiapine.
Type of intervention	Treatment.
Hypothesis/study question	The aim of the study was to explore the impact of side effect profiles of four atypical antipsychotics (olanzapine, quetiapine, risperidone and ziprasidone) on non-compliance, relapse and treatment cost in schizophrenia. In the study, the health benefits and costs achieved with olanzapine, risperidone and ziprasidone were compared to those achieved with quetiapine. The authors did not explicitly stated the perspective adopted for the economic analysis, but it would seem to have been the perspective of the hospital.
Economic study type	Cost-effectiveness analysis.
Study population	The study population comprised outpatients with schizophrenia who were taking oral conventional antipsychotics.
Setting	The setting was secondary care. The study was carried out in the UK.
Dates to which data relate	The effectiveness data were derived from a review of published studies conducted in the past 20 years. Literature data were supplemented by expert opinion, the dates of which were not provided. The cost data for the US were obtained from two studies published in 1996 and 2001, while the cost data for the UK were obtained from another study published in 2000. The price year was not reported.
Source of effectiveness data	The evidence for the final outcomes was derived from a review of published studies and reviews. It was supplemented by a two-round Delphi study, in which a panel of 25 experts on schizophrenia assessed the impact of different side effect profiles on non-compliance.
Modelling	A state-transition model was used to represent the relationship between compliance and relapse over a 1-year period following recovery from an episode of schizophrenia. This technique involved identifying clinically important events and defining them as health states. The model incorporated three such states, "well, compliant" (starting state), "well, not compliant" and "relapsed". A theoretical cohort of patients then moved cyclically from one health state to another, in cycles set at the end of the month, for one year. To allow for the possibility that the probabilities of becoming not compliant and/or relapsing vary over time, Weibull survival distributions were fitted to the relevant data for each of the transition probabilities.
Outcomes assessed in the review	The outcomes assessed in the review were: the non-compliance and relapse rates observed when there was an abrupt withdrawal of antipsychotic medication, the rate of recovered patients continuing treatment with atypical antipsychotics,

	and the relapse rates linked to a particular treatment period.
Study designs and other criteria for inclusion in the review	Longitudinal observational studies, carried out in North America, Europe and Australasia, of outpatients with schizophrenia who were taking oral conventional antipsychotics, and which reported time-specific non-compliance rates, were included in the review.
Sources searched to identify primary studies	MEDLINE, EMBASE and PsycINFO were searched for primary studies.
Criteria used to ensure the validity of primary studies	Not stated.
Methods used to judge relevance and validity, and for extracting data	Only those studies reporting a time-specific non-compliance rate were judged to be relevant.
Number of primary studies included	A total of 32 publications were included in the analysis.
Methods of combining primary studies	Survival analysis methods were used to summarise the data and estimate non-compliance rates after 3, 6 and 12 months' treatment with conventional antipsychotics.
Investigation of differences between primary studies	Not reported.
Results of the review	The estimated differential 1-year relapse rate of olanzapine compared to quetiapine was 6.1% (95% confidence interval, CI: 3.2 - 9.3; 99% CI: 2.3 - 11.1). This difference was highly significant as the 99% CI did not include zero. The estimated differential 1-year relapse rate of risperidone compared to quetiapine was 5.6% (95% CI: 2.7 - 9.3; 99% CI: 1.5 - 11.4). Again, this difference was highly significant. The estimated differential 1-year relapse rates of ziprasidone compared to quetiapine were small and statistically insignificant.
Methods used to derive estimates of effectiveness	A two-round Delphi study involving 25 leading European and North American experts on schizophrenia was undertaken. These experts were asked to assess the impact of different side effect profiles on non-compliance. Information on side-effect profiles for conventional and atypical antipsychotics, as derived from published studies and the Cochrane Collaboration Reviews, was given to each expert. The experts were blinded to the identities of the atypical antipsychotics (identified by fictitious names) and were presented in a balanced order. The experts were then asked to estimate, using the information supplied, an estimate of the "lowest likely", "most likely" and "highest likely" non-compliance rates after 3, 6 and 12 months' treatment for each atypical antipsychotic. Four weeks later, each expert was presented with all his estimates and those of the other experts (anonymously). Each expert was then asked to confirm or revise their initial estimates in the light of other experts' conclusions. This was done in order to bring the experts closer to a consensus.
Estimates of effectiveness and key assumptions	The experts concluded the following: the estimated non-compliance rates for all atypical antipsychotics profiles at 3, 6

	and 12 months were better than those derived from the literature for conventional antipsychotics; the estimated non-compliance rates of quetiapine and ziprasidone were practically equal; the non-compliance rates based on the profiles of olanzapine and risperidone were greater than those based on the profiles of quetiapine and ziprasidone; the difference between the two pairs (olanzapine, risperidone and quetiapine, ziprasidone) increased with the duration of treatment.
Measure of benefits used in the economic analysis	No summary benefit measure was used in the economic analysis. A cost-consequences approach was therefore adopted.
Direct costs	The resources and the quantities were not reported separately. The direct costs of the hospital were included in the analysis. For the US-based costs, the authors derived their cost data from two studies (see Other Publications of Related Interest). One study (Glazer and Ereshefsky) built an economic model of outpatient antipsychotic therapy in schizophrenic patients who had been admitted to hospital numerous times in order to estimate the 1-year direct costs. The other study (Rosenheck et al.) estimated the average cost of hospitalising a veteran administration patient on atypical antipsychotics. For the UK-based costs the authors derived their cost data from a study by Almond and O'Donnell (see Other Publications of Related Interest), who used a Markov model to compare the 5-year costs of olanzapine, risperidone and haloperidol in the treatment of schizophrenia in the UK. Discounting was unnecessary, as all the costs were incurred during one year, and was not conducted. The study reported the incremental costs of olanzapine, risperidone and ziprasidone over quetiapine. The price year was not reported.
Indirect Costs	The indirect costs were not included in the analysis.
Currency	US dollars ($) when the US data sets were used. UK pounds sterling () when the UK data sets were used.
Statistical analysis of costs	The costs were treated in a stochastic manner. The authors reported the mean incremental costs with their respective 95% and 99% CIs.
Sensitivity analysis	No sensitivity analyses were performed.
Estimated benefits used in the economic analysis	See the 'Effectiveness Results' section.
Cost results	The modelled estimates of difference of olanzapine from quetiapine in incremental 1-year per patient costs of differing side effect profiles were $530 (95% CI: 275 - 800; 99% CI: 200 - 960) for US costs and 630 (95% CI: 330 - 960; 99% CI: 235 - 1,140) for UK costs. The modelled estimates of difference of risperidone from quetiapine in incremental 1-year per patient costs of differing side effect profiles were $485 (95% CI: 235 - 800; 99% CI: 130 - 985) for US costs and 575 (95% CI: 280 - 960; 99% CI: 155 - 1,170) for UK costs. The modelled estimates of difference of ziprasidone from quetiapine in incremental 1-year per patient costs of differing side effect profiles were $45 (95% CI: -145 - 235; 99% CI: -240 - 320) for US costs and 50 (95% CI: -175 -

	275; 99% CI: -285 - 370) for UK costs. These differences were not statistically significant since both sets of CIs contained 0.
Synthesis of costs and benefits	The costs and benefits were not combined since a cost-consequences approach was taken.
Authors' conclusions	Differing side effect profiles of the newer antipsychotic agents were likely to lead to different compliance rates and, consequently, variation in the relapse rates. The authors also concluded that the cost implications of the heterogeneous clinical outcomes were considerable.
CRD COMMENTARY - Selection of comparators	The choice of quetiapine as the comparator was not explicitly justified, although it would appear to be one of the four atypical antipsychotics currently being prescribed. Thus, it represented common practice in the authors' setting. You should decide if the comparator represents current practice in your own setting.
Validity of estimate of measure of effectiveness	The authors did not state that a systematic review of the literature had been undertaken, reporting only that a review using three search engines had found 32 publications. However, even if a systematic review was not performed to identify relevant research and minimise biases, the review undertaken was quite thorough. Three search engines were used to identify relevant studies carried out in North America, Europe and Australasia within the past 20 years. Data from these 32 studies were then supplemented with data from 2 systematic reviews. Survival analysis methods were used to summarise the data and estimate non-compliance rates. However, this method was not reported clearly, and it would appear that no weighting scheme was applied to reflect differences in sample sizes. Even though an investigation of differences between the primary studies was not reported, the inclusion criteria for entry into the review were fairly narrow (longitudinal observational studies of outpatients with schizophrenia who were taking oral conventional antipsychotics, which reported a time-specific non-compliance rate). Thus, any differences between the primary studies should not have greatly affected the estimate of effectiveness. The data derived from the literature review were supplemented by expert opinion. A Delphi panel of 25 leading European and North American experts in the field was assembled to derive the impact of different side effect profiles on non-compliance. The authors took steps to avoid attrition between the two rounds and, at the end of the study, all 25 experts had participated. To minimise biases, all materials given to the experts were standardised and the experts were blinded to the identities of the four antipsychotic treatments. To bring experts closer to consensus, feedback comprised both the individual and group responses. Sampling variation and intra-individual uncertainty were taken into account by bootstrapping. Despite these strengths, the authors noted that the Delphi experts were not randomly selected, thus raising the possibility of being a biased sample of experts on the treatment of schizophrenia. However, the authors also pointed out, that there was no a priori reason to assume that any bias would be related to the views of the experts on the relationship between drug side effects and compliance.
Validity of estimate of measure of benefit	The authors did not derive a summary measure of health benefit. The analysis was therefore categorised as a cost-consequences analysis.
Validity of estimate of costs	Since the cost data were derived and combined from several studies, and the authors gave very few details of which costs had been included, it is not possible to say whether all the categories of cost and all relevant costs were included in the analysis. However, the authors did point out that the per patient cost of

	managing treatment-induced side effects was ignored in the model, as it was assumed to be the same for each of the four atypical antipsychotics studied. Therefore, it is unlikely that such an omission will have affected the authors' conclusions. The costs and the quantities were not reported separately and the price year was not reported. These two limitations weaken the generalisability of the results and hinder reflation exercises to other settings. The incremental costs were presented with their respective 95% CIs and 99% CIs, thus acknowledging uncertainty in the costs. Discounting was unnecessary, as all the costs were incurred in one year, and was not performed.
Other issues	The authors did not compare their findings with those from other studies. The issue of generalisability to other settings was not addressed, further hampering the generalisability of the authors' results. The authors do not seem to have presented their results selectively. The authors' conclusions reflect the scope of the analysis. The authors reported no further limitations to their study.
Implications of the study	The authors seem to suggest that the results should be confirmed in patient-based studies. If these confirm the authors' results it would imply that, for 1.5% of UK patients with schizophrenia, changing the medication to an atypical antipsychotic with a better side effect profile could realise savings of up to 1 million per annum in direct treatment costs.
Source of funding	Supported by AstraZeneca.
Bibliographic detail	Mortimer A, Williams P, Meddis D. Impact of side-effects of atypical antipsychotics on non-compliance, relapse and cost. Journal of International Medical Research 2003; 31(3): 188-196
Other publications of related interest	Lindstrom E, Bingefors K. Patient compliance with drug therapy in schizophrenia. Pharmacoeconomics 2000;18:105-24. Glazer W, Ereshefsky L. A pharmacoeconomic model for outpatient antipsychotic therapy in "revolving door" schizophrenic patients. Journal of Clinical Psychiatry 1996;57:337-45. Rosenbeck R, Leslie D, Sernyak M. From clinical trials to real-world practice: use of antipsychotic medication nationally in the department of Veteran Affairs. Medical Care 2001:39;302-8. Almond S, O'Donnell O. Cost analysis of the treatment of schizophrenia in the UK. Pharmacoeconomics 2000;17:383-9.
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Antipsychotic Agents /economics /therapeutic use; Benzodiazepines /economics /therapeutic use; Dibenzothiazepines /economics /therapeutic use; Great Britain; Health Care Costs; Humans; Patient Compliance; Piperazines /economics /therapeutic use; Recurrence; Research Support, Non-U.S. Gov't; Risperidone /economics /therapeutic use; Schizophrenia /drug therapy /economics; Thiazoles /economics /therapeutic use
Accession number	22003000956
Database entry date	30 April 2004
Record status	This is a critical structured abstract of an economic evaluation that meets the criteria for inclusion on NHS EED.

	Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Mortimer 2003: HEED record

Article Reference No	029507
Author	Mortimer A, Williams P, Meddis D
Article Title	Impact of side-effects of atypical antipsychotics on non-compliance, relapse and cost
Journal Name	The Journal of International Medical Research
Journal Date	2003
Journal Reference	31:188-196
Publication Status	Published in a journal of unknown status
Availability Details	Correspondence: A Mortimer, Department of Psychiatry, University of Hull, Willerby, Hull, UK (first-named author)
Source Of Article	O
Countries Of Authors	UK
Countries Applicable	UK, USA
Type Of Article	Applied study
Type Of Econ Eval	Cost analysis
Technology Assessed	Pharmaceutical
ATC Codes	N05A
ICD-9 Codes	295
Drug Names	OLANZAPINE; QUETIAPINE; RISPERIDONE; ZIPRASIDONE
Quantities of Resources Used	Observational data
Prices or Costs of Resources	'Ad Hoc' Estimation
Costs Included	Hospital costs;Direct provider/purchaser costs
Study Question	To explore the impact of side-effect profiles of four atypical antipsychotics (quetiapine, ziprasidone, olanzapine and risperidone) on non-compliance, relapse and treatment cost in schizophrenia. This was done through a state-transition model based on literature data supplemented by expert opinion.
Key Results	The estimated differential 1-year relapse rates (compared with quetiapine) were: olanzapine profile, mean 6.1% (95% CI, 3.2, 9.3); risperidone profile, mean 5.6% (95% CI, 2.7, 9.3); ziprasidone profile, mean 0.5% (95% CI, -1.7, 2.7). Thus, the difference between quetiapine and ziprasidone was small and statistically insignificant. The estimated relapse rates for olanzapine and risperidone were highly significant. The model found that quetiapine and ziprasidone were similar in estimated non-compliance and relapse rates. Olanzapine and risperidone had higher estimated non-compliance and relapse rates, and incremental, 1-year, per-patient direct costs, using US-based cost data, of approximately US$530 (95% confidence interval [CI] approximately US$275, US$800), and approximately US$485 (95%

	CI approximately US$235, US$800), respectively, compared with quetiapine. Thus, the incremental cost associated with the difference in side-effect profiles between quetiapine and ziprasidone was trivial. The less favourable side-effect profile of olanzapine, largely due to greater weight gain, was associated with an incremental, 1-year, per-patient cost of US$530 or £630 compared with quetiapine. The less favourable side-effect profile of risperidone, largely due to greater EPS liability, but also to prolactin elevation, was associated with an incremental, 1-year, per-patient cost of US$485 or £575 compared with quetiapine. Neither the 95% or 99% CIs for these incremental costs (for olanzapine and risperidone were significant. The authors conclude that the study shows that differing side-effect profiles of the newer antipsychotic agents are likely to lead to different compliance rates, and consequent variation in relapse rates.
Patient Group	Persons with schizophrenia.
Sponsor	Pharmaceutical industry
Keywords	Cost Analysis;Pharmaceutical;Schizophrenia;Modelling

Mould 2009: NHS EED record

N/A – Not identified in search of NHS EED

Mould 2009: HEED record

Article Reference No	080863
Author	Mould Q J, Contreras H I, Verduzco W, Mejia A J M, Garduno E J
Article Title	Cost-effectiveness simulation analysis of schizophrenia at the Instituto Mexicano del Seguro Social: Assessment of typical and atypical antipsychotics
Journal Name	Revista de Psiquiatria y Salud Mental
Journal Date	2009
Journal Reference	2(3):108-118
Source Of Article	O
Abstract	Introduction: Estimation of the economic costs of schizophrenia is a fundamental tool for a better understanding of the magnitude of this health problem. The aim of this study was to estimate the costs and effectiveness of five antipsychotic treatments (ziprasidone, olanzapine, risperidone, haloperidol and clozapine), which are included in the national formulary at the Instituto Mexicano del Seguro Social, through a simulation model. Methods: Type of economic evaluation: complete economic evaluation of cost-effectiveness. Study perspective: direct medical costs. Time horizon: 1 year. Effectiveness measure: number of months free of psychotic symptoms. Analysis: to estimate cost-effectiveness, a Markov model was constructed and a Monte Carlo simulation was carried out. Results: Effectiveness: the results of the Markov model showed that the antipsychotic with the highest number months free of psychotic symptoms was ziprasidone (mean 9.2 months). The median annual costs for patients using ziprasidone included in the hypothetical cohort was 194,766.6 Mexican pesos (MXP) (95% CI, 26,515.6-363,017.6 MXP), with an exchange rate of 1 Euro = 17.36 MXP. The highest costs in the probabilistic analysis were estimated for clozapine treatment (260,236.9 MXP). Conclusions: Through a probabilistic analysis, ziprasidone showed the lowest costs and the highest number of months free of psychotic symptoms and was also the most cos teffective antipsychotic observed in acceptability curves and net monetary benefits.
Keywords	Non-English Language - Spanish;Schizophrenia;Cost Effectiveness Analysis (CEA);Pharmaceutical

Obradovic 2007: NHS EED record

N/A – Not identified in search of NHS EED

Obradovic 2007: HEED record

Article Reference No	041856
Author	Obradovic M, Mrhar A, Kos M
Article Title	Cost-effectiveness of antipsychotics for outpatients with chronic schizophrenia
Journal Name	International Journal of Clinical Practice
Journal Date	2007
Journal Reference	61(12):1979-1988
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence: Mitja Kos, Faculty of Pharmacy, University of Ljubljana, Askerceva 7, 1000 Ljubljana, Slovenia. E-mail: mitja.kos@ffa.uni-lj.si
Cost Base Year	2005
Source Of Article	O
Countries Of Authors	Slovenia
Countries Applicable	Slovenia
Type Of Article	Applied study
Type Of Econ Eval	Cost consequences
Technology Assessed	Pharmaceutical
ATC Codes	N05A
ICD-9 Codes	295
Drug Names	AMISULPRIDE; ARIPIPRAZOLE; HALOPERIDOL; OLANZAPINE; QUETIAPINE; RISPERIDONE; ZIPRASIDONE
Prob. of Main Clinical Events	Observational data;Other literature review
Quantities of Resources Used	Judgement;Modelling
Prices or Costs of Resources	National Publication;'Ad Hoc' Estimation
Outcomes	Observational data;Other literature review;Modelling
Outcome Measure	Remissions within 1 year
Costs Included	Hospital costs;Direct provider/purchaser costs
Sensitivity Tested	Sensitivity tested
Quantitatively Reported	Quantitatively reported
Study Question	To evaluate the cost-effectiveness of alternative treatments for outpatients with chronic schizophrenia from the healthcare payer's perspective. A decision analysis was used to evaluate the cost-effectiveness of: amisulpride, aripiprazole, haloperidol (oral formulation), haloperidol (depot formulation), olanzapine, quetiapine, risperidone (oral formulation), risperidone (depot formulation) and ziprazidone

Key Results	The aim of this study was to evaluate the cost-effectiveness of alternative treatments for outpatients with chronic schizophrenia from the healthcare payer's perspective. The most effective treatment was the treatment with olanzapine, achieving 64.1% of patients in remission. The least effective was the treatment with quetiapine, where 32.7% of patients stayed in remission. Overall costs ranged from Euros 3,726.78 for haloperidol to Euros 8,157.03 for risperidone in depot formulation. Inpatient costs represented the major part of costs for most of antipsychotic drugs. Exceptions were risperidone in depot formulation and olanzapine, where inpatient cost represented 42.5% and 44.9% of total costs, respectively. Inpatient costs for haloperidol constituted 95.1% of total treatment costs. Typical antipsychotic drugs had substantially smaller outpatient costs compared with atypical antipsychotics; these costs constituted on average 6.5% and 37.9% of total costs. Strategies not eliminated by absolute or extended dominance were haloperidol, haloperidol decanoate and olanzapine. Amisulpride, ziprasidone, quetiapine and risperidone in depot formulation were absolutely dominated. Risperidone in oral formulation and aripiprazole were extendedly dominated by haloperidol decanoate and olanzapine. Sensitivity analysis showed that when the duration of hospitalisation reached 41 days haloperidol decanoate became the least expensive strategy, and the only non-dominated strategies were treatment with haloperidol decanoate and olanzapine. Assuming equal compliance rates for oral and depot formulations, haloperidol decanoate was dominated by oral haloperidol. The results of the model were sensitive to haloperidol rehospitalisation rate. When the rate was increased by 1% or more, risperidone became a non-dominated strategy. Treatment with aripiprazole and amisulpride was as effective as the treatment with olanzapine, and at the same time 25% cheaper in case of aripiprazole and 23% cheaper in case of amisulpride. The authors conclude that among second-generation antipsychotics, which have a better safety profile than first-generation antipsychotics, olanzapine and risperidone showed to be the most cost-effective treatment strategies for outpatient treatment of chronic schizophrenia.
Patient Group	Outpatients with chronic schizophrenia
Keywords	Modelling;Schizophrenia;Pharmaceutical;Cost Consequences Analysis;Cost Effectiveness - Methods Applied;Decision Analysis
Response to Articles	067425;067426

Kamal 2011: Economic analyses (economic burden/cost-of-illness)

Flynn 2008: NHS EED record

The cost of cerebral ischaemia
Flynn R W, MacWalter R S, Doney A S

Record status	This study has been evaluated by a health economist for CRD. This study is not an economic evaluation and has not received an abstract. It is considered to be a cost study and the bibliographic details are included here for information.
Bibliographic details	Flynn R W, MacWalter R S, Doney A S. The cost of cerebral ischaemia. Neuropharmacology 2008; 55(3): 250-256
Link to Pubmed record	18573263
Language	English
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Brain Ischemia /economics /epidemiology /mortality; Caregivers /economics; Cost of Illness; Costs and Cost Analysis; Delivery of Health Care /economics; Humans
Accession number	22008101681
Database entry date	2 March 2009

Flynn 2008: HEED record

N/A – Not identified in search of HEED

Payne 2002: NHS EED Record

N/A – Not identified in search of NHS EED

Brito 2011: Economic analyses (economic burden/cost-of-illness)

Shetty 2008: NHS EED record

Cost of care for new versus recurrent acute coronary syndrome patients
Shetty S, Halpern R, McCollam P L

Record status	This study has been evaluated by a health economist for CRD. This study is not an economic evaluation and has not received an abstract. It is considered to be a cost study and the bibliographic details are included here for information.
Bibliographic details	Shetty S, Halpern R, McCollam P L. Cost of care for new versus recurrent acute coronary syndrome patients . Journal of Medical Economics 2008; 11: 81-99
Language	English
Subject index terms status	Subject indexing assigned by CRD
Subject index terms	Acute Coronary Syndrome; Cost of Illness; Health Care Costs; Humans
Accession number	22008100375
Database entry date	30 September 2008

Shetty 2008: HEED record

N/A – Not identified in search of HEED

Taylor 2007: NHS EED record

Acute coronary syndromes in Europe: 1-year costs and outcomes

Taylor M J, Scuffham P A, McCollam P L, Newby D E

Record status	This study has been evaluated by a health economist for CRD. This study is not an economic evaluation and has not received an abstract. It is considered to be a cost study and the bibliographic details are included here for information.
Bibliographic details	Taylor M J, Scuffham P A, McCollam P L, Newby D E. Acute coronary syndromes in Europe: 1-year costs and outcomes. Current Medical Research and Opinion 2007; 23(3): 495-503
Link to Pubmed record	17355731
Language	English
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Adult; Aged; Analysis of Variance; Angina, Unstable /diagnosis /economics /mortality /therapy; Angioplasty, Transluminal, Percutaneous Coronary /economics /mortality; Cause of Death; Combined Modality Therapy; Coronary Artery Bypass /economics /mortality; Cost of Illness; Drug Therapy, Combination; Europe /epidemiology; Female; Health Care Costs /statistics & numerical data; Health Care Surveys; Hospitalization /economics /statistics & numerical data; Humans; Male; Middle Aged; Myocardial Infarction /diagnosis /economics /mortality /therapy; Probability; Quality of Health Care; Severity of Illness Index; Survival Analysis; Treatment Outcome
Accession number	22007000717
Database entry date	24 April 2007

Taylor 2007: HEED record

N/A – Not identified in search of HEED

Turpie 2006: NHS EED record

Burden of disease: medical and economic impact of acute coronary syndromes
Turpie A G

Record status	This study has been evaluated by a health economist for CRD. This study is not an economic evaluation and has not received an abstract. It is considered to be a cost study and the bibliographic details are included here for information.
Bibliographic details	Turpie A G. Burden of disease: medical and economic impact of acute coronary syndromes. American Journal of Managed Care 2006; 12(16 Supplement): S430-S434
Link to Pubmed record	17203987
Language	English
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Acute Disease; Cardiovascular Diseases /economics; Cost of Illness; Humans; United States
Accession number	22007006211
Database entry date	25 July 2007

Turpie 2006: HEED record

N/A – Not identified in search of HEED

Dasari 2011: Economic analyses (economic burden/cost-of-illness)

Yu 2008: NHS EED record

The costs of Crohn's disease in the United States and other Western countries: a systematic review

Yu A P, Cabanilla L A, Wu E Q, Mulani P M, Chao J

Record status	This study has been evaluated by a health economist for CRD. This study is not an economic evaluation and has not received an abstract. It is considered to be a cost study and the bibliographic details are included here for information.
Bibliographic details	Yu A P, Cabanilla L A, Wu E Q, Mulani P M, Chao J. The costs of Crohn's disease in the United States and other Western countries: a systematic review. Current Medical Research and Opinion 2008; 24(2): 319-328
Link to Pubmed record	18067689
Language	English
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Crohn Disease /economics /epidemiology; Europe /epidemiology; Health Care Costs /statistics & numerical data; Health Resources /economics; Hospitalization /economics; Humans; Prevalence; United States /epidemiology
Accession number	22008006127
Database entry date	3 February 2009

Yu 2008: HEED record

Article Reference No	041912
Author	Yu A P, Cabanilla L A, Wu E Q, Mulani P M, Chao J
Article Title	The costs of Crohn's disease in the United States and other Western countries: a systematic review
Journal Name	Current Medical Research and Opinion
Journal Date	2008
Journal Reference	24(2):319-328
Publication Status	Published in a peer reviewed journal
Availability Details	Correspondence: Andrew P Yu, PhD, Analysis Group, Inc., 111 Huntington Avenue, 10th Floor, Boston, MA 02199, USA. E-mail: ayu@analysisgroup.com
Source Of Article	O
Countries Of Authors	USA
Countries Applicable	International
Type Of Article	Review of applied studies
Type Of Econ Eval	Cost analysis
ICD-9 Codes	556; 569
Quantities of Resources Used	Systematic review and/or meta analysis
Prices or Costs of Resources	'Ad Hoc' Estimation
Costs Included	Hospital costs;Direct provider/purchaser costs;Indirect costs
Abstract	Objective: To conduct a critical and systematic literature review of the costs of Crohn's disease (CD) in Western industrialized countries. Research Design and Methods: Studies published in English that described the cost of CD in Western industrialized countries were identified using three major databases (Medline, EMBASE, and ISI Web of Science). Studies were reviewed and rated based on their relevance to cost of illness and the reliability of the estimates. All costs were adjusted for inflation to 2006 values. Results: Estimated direct medical costs were $18,022-18,932 per patient with CD per year in the United States, and euro 2898-6960 in other Western countries. Hospitalizations accounted for 53-66% of direct medical costs, with an average cost-per-hospitalization of $37,459 in the United States. Estimated indirect costs accounted for 28% of the total cost in the United States and 64-69% in Europe. Costs differed greatly by disease severity. Costs of patients with severe disease were 3- to 9-fold higher than patients in remission. Direct medical costs in the United States for patients in the top 25% of total costs averaged $60,582 per year; costs of patients in the top 2% averaged more than $300,000 per year. Combining prevalence rates, the total economic burden of CD was $10.9-15.5 billion in the United States and euro 2.1-16.7 billion in Europe. Limitations: This

	review is limited by the research quality and variations of the individual studies reviewed, and only includes English articles. Conclusions: This updated literature synthesis demonstrated the substantial total cost burden of CD, of which hospitalizations accounted for more than half of direct medical costs. Reproduced by kind permission of the journal of Current Medical Research and Opinion
Study Question	To conduct a critical and systematic literature review of the costs of Crohn's disease (CD) in Western industrialized countries. Studies published in English that described the cost of CD in Western industrialized countries were identified using three major databases and studies were reviewed, and rated, based on their relevance to cost of illness and the reliability of the estimates
Key Results	A total of 30 relevant articles were identified for review, of which 22 were original and unique studies with primary data analysis. Four articles were further excluded because they only examined costs or utilization associated with a specific treatment, leaving a total of 18 articles that formed the basis of the review. There were substantial variations among the studies in terms of cost-reporting method. Estimated direct medical costs were US$18,022-18,932 per patient with Crohn's disease (CD) per year in the United States, and Euros 2898-Euros 6960 in other Western countries. Hospitalizations accounted for 53-66% of direct medical costs, with an average cost-per-hospitalization of US$37,459 in the United States. Estimated indirect costs accounted for 28% of the total cost in the United States and 64-69% in Europe. Costs differed greatly by disease severity. Costs of patients with severe disease were 3- to 9-fold higher than patients in remission. Direct medical costs in the United States for patients in the top 25% of total costs averaged US$60,582 per year; costs of patients in the top 2% averaged more than US$300,000 per year. Combining prevalence rates, the total economic burden of CD was US$10.9-US$15.5 billion in the United States and Euros 2.1-16.7 billion in Europe. In the United States, combining reliable direct medical costs and indirect cost estimates, the total costs of CD per patient per year was US$25 282ûUS$26 192, of which indirect costs accounted for approximately 28% of the total costs. Using the estimated prevalence rate of CD in North America of 144û198/100 000, the total direct medical costs of CD were estimated to be US$7.8ûUS$11.2 billion in 2006. The authors conclude that there is a substantial total cost burden of CD, of which hospitalizations accounted for more than half of direct medical costs.
Patient Group	Patients with Crohn's disease
Sponsor	Pharmaceutical industry
Keywords	Inflammatory Bowel Disease;Systematic Review;Cost of Illness;Crohn's Disease

Wildschut 2011: Economic analyses (economic burden/cost-of-illness)

N/A – No relevant and potentially useful economic analyses identified

Komossa 2011: Economic analyses (economic burden/cost-of-illness)

Genduso 2007: NHS EED record

Cost of illness studies for schizophrenia: components, benefits, results, and implications
Genduso L A, Haley J C

Record status	This study has been evaluated by a health economist for CRD. This study is not an economic evaluation and has not received an abstract. It is considered to be a cost study and the bibliographic details are included here for information.
Bibliographic details	Genduso L A, Haley J C. Cost of illness studies for schizophrenia: components, benefits, results, and implications. American Journal of Managed Care 1997; 3(6): 873-877
Link to Pubmed record	10170292
Language	English
Subject index terms status	Subject indexing assigned by CRD
Subject index terms	Australia; Cost of Illness; Great Britain; Health Care Costs /statistics & numerical data /trends; Health Services Research; Humans; Netherlands; Puerto Rico; Schizophrenia /economics; United States
Accession number	21997001430
Database entry date	31 March 1999

Genduso 2007: HEED record

N/A – Not identified in search of HEED

Knapp 2004: NHS EED record

The global costs of schizophrenia
Knapp M, Mangalore R, Simon J

Record status	This study has been evaluated by a health economist for CRD. This study is not an economic evaluation and has not received an abstract. It is considered to be a review article and the bibliographic details are included here for information.
Bibliographic detail	Knapp M, Mangalore R, Simon J. The global costs of schizophrenia. Schizophrenia Bulletin 2004; 30(2): 279-293
Link to Pubmed record	15279046
Language	English
Subject index terms status	Subject indexing assigned by NLM
Subject index terms	Africa; Australia; Canada; Chronic Disease; Cost of Illness; Criminal Law /economics; Europe; Family /psychology; Family Health; Health Care Costs; Health Status; Humans; Schizophrenia /economics; United States
Accession number	22004006547
Database entry date	14 November 2005

Knapp 2004: HEED record

Article Reference No	066501
Author	Knapp M, Mangalore R, Simon J
Article Title	The global costs of schizophrenia
Journal Name	Schizophrenia Bulletin
Journal Date	2004
Journal Reference	30(2):279-293
Publication Status	Published in a peer reviewed journal
Availability Details	Reprints: Dr Martin Knapp, Director, Centre for the Economics of Mental Health, Health Services Research Department, Box PO24, Institute of Psychiatry, De Crespigny Park, London SE5 8AF. E-mail: cemh@iop.kcl.ac.uk
Source Of Article	O
Countries Of Authors	UK
Countries Applicable	Mexico, Nigeria, Puerto Rico, Australia, Belgium, Canada, Denmark, France, Germany, Hungary, the Netherlands, Norway, Sweden, UK, USA, Italy, Spain, Switzerland
Type Of Article	Review of applied studies
Type Of Econ Eval	Cost of illness
Technology Assessed	Pharmaceutical;Rehabilitation / physical therapy;Procedures;Education;Care;Counselling
ATC Codes	N05A; N05B; N05C
ICD-9 Codes	295; V40
Non-Drug Technologies Assessed	Institutionalisation, ambulatory visits
Quantities of Resources Used	Observational data;Systematic review and/or meta analysis
Prices or Costs of Resources	National Publication;Local Standard Costs;Local Standard Prices
Costs Included	Patient costs;Hospital costs;Direct provider/purchaser costs;Non health service public expenditure;Indirect costs
Study Question	Schizophrenia is a chronic disease associated with a significant and long-lasting burden, not only for patients but also for families, other caregivers and the wider society. Many national and local studies have sought to estimate the societal burden of the illness - or some components of it - in monetary terms. Findings vary. The aim of this systematic review of the literature was to locate all existing international estimates to date. Sixty-two relevant studies were found and summarised. Within- and between-country differences were analysed descriptively.
Key Results	The authors' systematically reviewed the literature to locate all existing international estimates to date. Sixty-two relevant studies were found and summarized. Despite the wide diversity of data sets

	and methods applied, all cost-of-illness estimates highlight the heavy societal burden of schizophrenia. However, this full cost is rarely fully appreciated by health care decision-makers or other stakeholders. Schizophrenia is a chronic illness and its costs tend to persist. The impact of schizophrenia on health care budgets is substantial, typically between 1.5% and 3% of total national health care expenditures. Generally, between 1/3 and 2/3 of the total health care cost of schizophrenia is for hospitalisation, even in countries that have already substantially reduced their inpatient provision. Less readily observed, but often no less important, are costs to other care organisations and public sector bodies, notably social service agencies, housing departments and the criminal justice system. A proportion of the aggregate costs of schizophrenia is borne by charities, non-governmental organisations and private for-profit bodies, either as the providers of services or as the funders. There are often substantial hidden or indirect costs of schizophrenia to people with schizophrenia themselves, to their families and other caregivers and to the wider society. Employment difficulties are very common among people with schizophrenia, mortality rates are high and substantial family burden has been reported. Perhaps most pertinent, however, are those costs experienced by people with schizophrenia linked to the distress, pain and impoverished quality of life that so often accompany the illness. These are not measurable in monetary terms, but they may provide another reason why more must be done to improve treatments for people with schizophrenia. Based on these findings, the authors conclude that such information helps us to understand the health, health care, economic and policy importance of schizophrenia and to better interpret and explain the large within- and across-country differences that exist.
Patient Group	Patients with schizophrenia.
Keywords	Cost of Illness;Schizophrenia;Systematic Review

Appendix 6: Yields of eligible records from original searches of Medline, Embase and Central

Table A6.1. Eligible economic evaluations (reviews with one or more eligible economic evaluations only)

First author/ year	*Total eligible records*	*Medline* (Exc RCT filter)*	*Medline* (Inc RCT filter)*	*Embase* (Exc RCT filter)*	*Embase* (Inc RCT filter)*	*Central*
Smith 2011	1	1	1	-	-	1
Kamal 2011	1	1	-	1	-	-
Martin 2011	1	-	-	-	-	0
Anijeet 2011	1	1	0	1	0	0
Brito 2011	3	-	-	3	1	1
Dasari 2011	6	5	1	5	4	1
Gaitán 2011	2	2	2	2	2	-
Wildschut 2011	1	1	1	-	-	1
Komossa 2011	11	-	-	-	-	-
Taylor 2011	24	18	11	20	8	3

* Numbers (out of total eligible records – NHS EED and HEED records combined, duplicates removed) of eligible economic evaluations located by re-running original search strategies designed to locate studies of effects.

- Original search not conducted for intervention review or insufficient details in published review to replicate search streategy.

Table A6.2. Eligible economic analyses (economic burden/cost-of-illness – selected reviews only)

First author/ year	*Total records*	*Medline* (Exc RCT filter)*	*Medline* (Inc RCT filter)*	*Embase* (Exc RCT filter)*	*Embase* (Inc RCT filter)*	*Central**
Kamal 2011	19	0	-	0	-	-
Brito 2011	17	-	-	0	0	0
Dasari 2011	16	0	0	0	0	0
Wildschut 2011	0	-	-	-	-	-
Komossa 2011	65	-	-	-	-	-

* Numbers (out of total eligible records – NHS EED and HEED records combined, duplicates removed) of eligible economic evaluations located by re-running original search strategies designed to locate studies of effects.

- Original search not conducted for intervention review or insufficient details in published review to replicate search streategy.

Appendix 7: Assessments of study limitations: eligible economic evaluations

[#Incomplete: assessments complieted for first 4 of 21 economic evaluations]

Kamal 2011

Inoue 2006

Study limitations (the level of methodological quality)	Yes/ Partly /No/ Unclear/ NA	Comments
Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	The model type (Markov model) and its structural aspects appear to be consistent with a coherent theory of the health condition under evaluation. The selection of health states appears to be based on and consistent with the underlying biological processes of the health issue under study and the potential benefits and adverse consequences of use of cilostazol (versus aspirin and no prophylaxis) for the secondary prevention of cerebral infarction.
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	The time horizon was not reported but it would appear to relate to the patients' lifetime. In this case, the time horizon is

		sufficient to include all relevant costs and outcomes.
Are all important and relevant health outcomes included?	Partly	Outcomes assessed in the analysis were: rate of cerebral infarction recurrence without prophylaxis, relative risk of cerebral infarction recurrence, the rate of intra- and extra-cranial bleeding, mortality due to cerebral infarction, all other causes of mortality, and relative risk of mortality after recurrence by different levels of severity, as determined by the Barthel Index. The analysis omits other potential adverse effects that were assessed in the corresponding Cochrane review: gastrointestinal haemorrhage, headache, gastrointestinal intolerance, palpitation, dizziness, tachycardia, precipitation of angina, and cardiac failure. However, the omission of these potential adverse effects would be unlikely to change the cost-effectiveness results, since the Cochrane review found no evidence for differences between cilostazol

		and aspirin with respect to these potential adverse effects. As reported, there was an imbalance in the quantity of information used to populate the model parameters relating to different treatments, since only one trial assessed cilostazol for the prevention of cerebral infarction recurrences.
Are the estimates of baseline health outcomes from the best available source?	Partly	Estimates of baseline health outcomes are not derived from a systematic review but are likely to reflect outcomes for the relevant group of patients. Natural death rate at each stage (Markov cycle) was derived from Japanese life tables, while mortality rates after cerebral infarction recurrence were derived from data from a Japanese prefecture.
Are the estimates of relative treatment effects from the best available source?	Unclear	The authors did not report that a systematic review of the literature had been undertaken to identify evidence for relative treatment effects. However, the authors used a meta-analysis and a double-blind randomised controlled trial to derive the

		recurrence rates for stroke and adverse events, and the results from one trial to derive the rates of haemorrhagic adverse events. It is difficult to assess the extent to which estimates of relative treatment effects used in the analysis are similar in magnitude to those estimated in the corresponding Cochrane review without collecting unreported additional data from authors of the economic evaluation and undertaking further secondary analyses to compare these data with estimates reported in the Cochrane review.
Are all important and relevant costs included?	Yes	All important and relevant resource use and costs appear to be included given the perspective and the research question under consideration.
Are the estimates of resource use from the best available source?	Unclear	Quantities of resource use were not reported separately from costs. The authors did not report that a systematic review of the literature had been undertaken to identify evidence for relative resource use (re. relative treatment effects). However, the

		authors used a meta-analysis and a double-blind randomised controlled trial to derive the recurrence rates for stroke and adverse events, and the results from one trial to derive the rates of haemorrhagic adverse events.
Are the unit costs of resources from the best available source?	Yes	Quantities of resource use appear to have been valued using up-to-date unit costs obtained from published sources relevant to the study setting. The costs of the drugs were derived from official reimbursement price lists. The costs of treating intracranial haemorrhage due to recurrence were derived from a published study. The costs of long-term care were derived from the Japanese Ministry of Health, Labour, and Welfare. Since the costs were incurred over the lifetime of the patient, the costs were appropriately discounted at an annual rate of 3%.
Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Appropriate incremental results are presented.
Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	One-way sensitivity analyses were performed on all of the main parameters of the analysis,

		except utility values. The parameters were varied within a 50% decrease or increase from the base values. For utility values, the effect of varying the estimates was determined using Monte Carlo simulation, which randomly extracted the utility value for each Barthel Index (BI) category from a uniform distribution and had the range of each BI category as the upper and lower limit. There was no investigation of structural uncertainty.
Is there no potential conflict of interest?	No	Clear financial conflicts of interest are declared. The economic evaluation was sponsored by industry (Otsuka Pharamceutical Co. Ltd, Otsuka, Japan).
Overall assessment: Minor limitations.		
Other comments: The study fails to meet one or more quality criteria but it appears this is unlikely to change the conclusions with respect to incremental costs or cost effectiveness.		

Brito 2011

Latour-Perez 2009

Study limitations (the level of methodological quality)	**Yes/ Partly /No/ Unclear/ NA**	**Comments**
Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	The model type (Markov model) and its structural aspects appear to be consistent with a coherent theory of the health condition under evaluation. The selection of health states appears to be based on and consistent with the underlying biological processes of the health issue under study and the potential benefits and adverse consequences of use of subcutaneous (SC) fondaparinux with SC enoxaparin in the treatment of patients with non ST-elevation myocardial infarction.
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	The time horizon related to the patients' lifetime. A lifetime time horizon is sufficient to include all relevant costs and outcomes.
Are all important and relevant health outcomes included?	Yes	Outcomes assessed in the analysis were: (in the first one

		month cycle) therapeutic procedures (percutaneous revascularization, coronary bypass graft) and adverse events (major bleeding, fatal or non-fatal MI); (in all subsequent cycles) age related death and cardiac events (either fatal or non-fatal). The analysis therefore appears to include all important and relevant categories of health outcomes that were assessed in the corresponding Cochrane review.
Are the estimates of baseline health outcomes from the best available source?	Partly	Estimates of baseline health outcomes are not derived from a systematic review but are likely to reflect baseline health outcomes for the relevant group of patients.
Are the estimates of relative treatment effects from the best available source?	Partly	The authors did not report that a systematic review of the literature had been undertaken to identify evidence for relative treatment effects. However, the authors utilised comparative effectiveness and safety data collected from the OASIS-5 trial (Yousef 2006) to populate corresponding parameters in the

		model. The authors also report that selection of data sources was "performed in a non-systematic way, and conditioned on the adequacy of the data to the decision problem. Data from systematic reviews were preferred when available; however, these were scarce." It is difficult to assess the extent to which estimates of relative treatment effects used in the analysis are similar in magnitude to those estimated in the corresponding Cochrane review without undertaking further secondary analyses to compare these data with estimates reported in the Cochrane review.
Are all important and relevant costs included?	Yes	All important and relevant resource use and costs appear to be included given the perspective and the research question under consideration.
Are the estimates of resource use from the best available source?	Unclear	Quantities of resource use were not reported separately from costs. The authors did not report that a systematic review of the literature had been undertaken to identify evidence for relative

		treatment effects. However, the authors utilised comparative effectiveness and safety data collected from the OASIS-5 trial (Yousef 2006) to populate corresponding parameters in the model. The authors also report that selection of data sources was "performed in a non-systematic way, and conditioned on the adequacy of the data to the decision problem. Data from systematic reviews were preferred when available; however, these were scarce."
Are the unit costs of resources from the best available source?	Yes	Quantities of resource use appear to have been valued using up-to-date unit costs obtained from published sources relevant to the study setting. Data on the healthcare costs were obtained from Spanish studies. All costs were updated to the year 2006 using the Spanish medical inflation index.
Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Appropriate incremental results are presented.
Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Both one-way and probabilistic sensitivity analyses were performed on all of the main

		parameters of the analysis. There was no investigation of structural uncertainty.
Is there no potential conflict of interest?	Yes	The authors declare that they have no financial conflicts of interest.
Overall assessment: Minor limitations.		
Other comments: The study fails to meet one or more quality criteria but it appears this is unlikely to change the conclusions with respect to incremental costs or cost effectiveness.		

Maxwell 2009

Study limitations (the level of methodological quality)	**Yes/ Partly /No/ Unclear/ NA**	**Comments**
Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	The model type (decision tree) and its structural aspects appear to be consistent with a coherent theory of the health condition under evaluation. The selection of treatment pathways appears to be based on and consistent with the underlying biological processes of the health issue under study and the potential

		benefits and adverse consequences of use of anticoagulation strategies in the treatment of patients with non ST-elevation myocardial infarction. A decision tree was used to synthesise the data from published clinical trials for the four treatment regimens. For each treatment arm of the decision tree, a patient followed a treatment path either with or without complications.
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Unclear	The time horizon was not reported.
Are all important and relevant health outcomes included?	Unclear	The sole measure of treatment benefit assessed in the analysis was additional patients treated without complications (relative complication rates between the anticoagulation strategies compared). Further details of complications assessed are not available in either the NHS EED record or HEED record and the full-text article was not available within local library resources. The authors justified the focus on this measure of treatment benefit on the basis that this was the only

		clinically significant difference between the treatments found in source randomized controlled trials.
Are the estimates of baseline health outcomes from the best available source?	Unclear	Details of baseline health outcomes are not available in either the NHS EED record or HEED record and the full-text article was not available within local library resources.
Are the estimates of relative treatment effects from the best available source?	Unclear	The NHS EED record states that "clinical evidence was identified from recent available anticoagulation studies that compared the four strategies." The analysis utilised clinical evidence collected from three RCTs, including the OASIS-5 trial (Yousef 2006), to populate corresponding parameters in the model. It is not possible to assess the extent to which estimates of relative treatment effects (complication rates) used in the analysis are similar in magnitude to those estimated in the corresponding Cochrane review without collecting unreported additional data from authors of the economic evaluation and

		undertaking further secondary analyses to compare these data with estimates reported in the Cochrane review. Additionally, the Cochrane review did not include evidence relating to one of the four anticoagulation strategies assessed in this economic evaluation (bivalirudin alone).
Are all important and relevant costs included?	Yes	All important and relevant resource use and costs appear to be included given the perspective and the research question under consideration. Included cost categories were the treatment, drug acquisition, and complications of the four anticoagulation strategies assessed.
Are the estimates of resource use from the best available source?	Unclear	Quantities of resource use were not reported separately from costs. It is unclear, based on the NHS EED and HEED records, whether a systematic review of the literature had been undertaken to identify evidence for relative treatment effects (although this appears unlikely). The NHS EED record states that

		"The resource use data were from published clinical trials that sampled moderate-to-high-risk patient populations." It therefore appears that the analysis utilised evidence collected from three RCTs, including the OASIS-5 trial (Yousef 2006), to populate resource use parameters in the model.
Are the unit costs of resources from the best available source?	Partly	Quantities of resource use appear to have been valued using up-to-date unit costs obtained from published sources relevant to the study setting. However, wholesale costs and Medicare reimbursement data were used and these might not represent the costs for all patients in the population. The authors did not report any discounting of the costs and they did not state the price year.Drug acquisition costs were from the wholesaler-purchasing database of the Virginia Commonwealth University Medical Center. The major complication costs were based on diagnosis-related group data. Physician fees were

		estimated by assigning a Current Procedural Terminology code to all complications. The minor complication (bleeding) costs were from hospital blood bank reports.
Is an appropriate incremental analysis presented or can it be calculated from the data?	Unclear	It is not possible to assess this with confidence based on NHS EED and HEED records alone.
Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	One-way, two-way, and probabilistic sensitivity analyses were performed. The results were presented in a tornado diagram and a cost-effectiveness acceptability curve. Scattergrams were also generated from 100,000 Monte Carlo simulations. NHS EED and HEED do not indicate that investigation of structural uncertainty was undertaken.
Is there no potential conflict of interest?	Unclear	The source of funding was not reported.
Overall assessment: An overall assessment cannot be made with confidence based on NHS EED and HEED records alone.		
Other comments: None.		

Sculpher 2009

Study limitations (the level of methodological quality)	**Yes/ Partly /No/ Unclear/ NA**	**Comments**
Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	The model type (Markov model) and its structural aspects appear to be consistent with a coherent theory of the health condition under evaluation. The selection of health states appears to be based on and consistent with the underlying biological processes of the health issue under study and the potential benefits and adverse consequences of use of subcutaneous (SC) fondaparinux with SC enoxaparin in the treatment of patients with non ST-elevation myocardial infarction.
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	The time horizon related to the patients' lifetime. A lifetime time horizon is sufficient to include all relevant costs and outcomes.
Are all important and relevant health outcomes included?	Yes	Outcomes assessed in the analysis were: fatal or nonfatal

		prognostic (myocardial infarction and/or stroke) events and/or major and minor bleeds. The analysis therefore appears to include all important and relevant categories of major health outcomes that were assessed in the corresponding Cochrane review.
Are the estimates of baseline health outcomes from the best available source?	Partly	Estimates of baseline health outcomes are not derived from a systematic review but appear to reflect baseline health outcomes for the relevant group of patients. Probabilities of clinical events are based on Weibull3 risk equations fitted to OASIS-5 trial data (Yousef 2006). The hazard of each event is estimated as a function of treatment and baseline covariates.
Are the estimates of relative treatment effects from the best available source?	Partly	The authors utilised comparative effectiveness and safety data collected from the OASIS-5 trial (Yousef 2006) to populate corresponding parameters in the model. Probabilities of clinical events are based on Weibull3 risk equations fitted to OASIS-5 trial data (Yousef 2006). The hazard of

		each event is estimated as a function of treatment and baseline covariates. It is difficult to assess the extent to which estimates of relative treatment effects used in the analysis are similar in magnitude to those estimated in the corresponding Cochrane review without undertaking further secondary analyses to compare these data with estimates reported in the Cochrane review.
Are all important and relevant costs included?	Yes	All important and relevant resource use and costs appear to be included given the perspective and the research question under consideration.
Are the estimates of resource use from the best available source?	Partly	The authors utilised resource use measures collected prospectively in the OASIS-5 trial (Yousef 2006) to populate corresponding resource use parameters in the model. The main categories of resource use were: drugs, concomitant medications, and inpatient days relating to fatal or nonfatal prognostic (myocardial infarction and/or stroke) events and/or major and minor bleeds.

Are the unit costs of resources from the best available source?	Yes	Quantities of resource use appear to have been valued using up-to-date unit costs obtained from published sources relevant to the study setting. Data on the healthcare costs were obtained from Spanish studies. All costs were updated to the year 2006 using the Spanish medical inflation index. The authors state that: "The base-case analysis uses resource use data from the 759 US patients which are valued using US costs, largely based on the Perspective Comparative Database (Premier Inc, Charlotte, NC), a HIPPA compliant database of approximately 500 hospitals from all regions of the United States… The database contains patient-level data derived from hospital accounting systems. It includes billing records for everything that happens to patients while admitted to hospital: medical and pharmacy files of all billed items, including medications, laboratory and diagnostic procedures, therapeutic services, and primary

		and secondary diagnoses. These cost estimates are based on all discharge data for 2003 to 2005 and reflect total costs (fixed and variable) to the hospital. Daily room costs are included for inpatient interventions. In the case of procedures and interventions, fees to medical professionals are estimated using the Integrated Healthcare Information Services National Managed Care Benchmark Database. Drug costs are based on wholesale acquisition costs (WAC). Blood transfusion costs are from published sources. Regression modeling is used to estimate the mean cost, excluding the study drug acquisition costs, of (1) patients without clinical events, and (2) the additional cost associated with each event over 180 days…Study drug costs were based on the mean dosage in OASIS-5 and the mean therapy duration in US trial patients. In the base case, these costs are based on WAC. The timing of potential generic brands of study

		drugs is speculative, but an alternative scenario tests the impact of drug pricing."
Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Appropriate incremental results are presented.
Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Both one-way and probabilistic sensitivity analyses were performed on all of the main parameters of the analysis. There was no investigation of structural uncertainty.
Is there no potential conflict of interest?	Yes	The economic evaluation was sponsored by industry (GlaxoSmithKline R&D, Upper Merion, PA, USA). However, the authors declare that: "The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript and its final contents."
Overall assessment: Minor limitations.		
Other comments: The study fails to meet one or more quality criteria but it appears this is unlikely to change the conclusions with respect to incremental costs or cost effectiveness.		

Dasari 2011

Duepree 2002

Study limitations (the level of methodological quality)	Yes/ Partly /No/ Unclear/ NA	Comments
Does the model structure adequately reflect the nature of the health condition under evaluation?	N/A	The economic evaluation was based on data from a single clinical study (retrospective, non-randomised trial with concurrent controls) and did not extrapolate treatment outcomes or costs beyond the study context or follow-up period.
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	The time horizon is arguably too short to capture all important differences in costs and outcomes. However, whilst it may be argued that comprehensive evaluation of these two types of surgery would require a longer follow-up, the focus of this economic evaluation is placed on investigating differences in perioperative costs and outcomes, including short-term (30 day) re-operation rates for disease recurrence, which is a

		similar focus to that of the corresponding Cochrane review.
Are all important and relevant health outcomes included?	Yes	Health outcomes assessed in the economic evaluation were: mortality, rate of conversion, operating time, intraoperative blood loss, postoperative recovery times, intraoperative and postoperative complications rates, time taken to return to work. The analysis therefore appears to include all important and relevant categories of major health outcomes that were assessed in the corresponding Cochrane review, with the exception of postoperative pain.
Are the estimates of baseline health outcomes from the best available source?	No	Estimates of baseline health outcomes are, in effect, derived from the control arm of the study, not using a systematic review. These estimates may or may not reflect baseline health outcomes in other populations of patients requiring surgical resection for ileocecal Crohn's disease.
Are the estimates of relative treatment effects from the best available source?	No	The authors utilised comparative effectiveness data collected from a single clinical study (retrospective, non-randomised

		trial with concurrent controls). It is difficult to assess the extent to which estimates of relative treatment effects used in the analysis are similar in magnitude to those estimated in the corresponding Cochrane review without undertaking further secondary analyses to compare these data with estimates reported in the Cochrane review. However, the direction of estimates of relative treatment effects appear, in general, to be similar to those reported in the corresponding Cochrane review.
Are all important and relevant costs included?	Yes	All important and relevant resource use and costs appear to be included given the perspective and the research question under consideration.
Are the estimates of resource use from the best available source?	Partly	The authors utilised resource use measures collected a single clinical study (retrospective, non-randomised trial with concurrent controls). The resource use measures include laboratory services, pharmacy, radiology, anaesthesia, operating room and hospital length of stay, and

		disposable operating equipment. For most included measures of resource use, it is unclear whether the estimates are similar in magnitude to the best available estimates, since quantities of resource use are not reported separately from cost estimates. Operative time and hospital length of stay estimates are in the same direction as corresponding estimates reported in the Cochrane review.
Are the unit costs of resources from the best available source?	N/A	Hospital costs per patient were calculated using actual data provided by the hospital; therefore unit costs are not reported separately from cost estimates.
Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Appropriate incremental results are presented for both costs and effects.
Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No sensitivity analyses were performed.
Is there no potential conflict of interest?	Unclear	The published report does not indicate whether or not there are financial conflicts of interest,
Overall assessment: Potentially serious limitations.		

Other comments: The study fails to meet one or more quality criteria and this could change the conclusions with respect to incremental costs and/or incremental effectiveness. See NHS EED structured abstract record for detailed commentary regarding potentially serious limitations of this study.

Maartense 2006

Study limitations (the level of methodological quality)	**Yes/ Partly /No/ Unclear/ NA**	**Comments**
Does the model structure adequately reflect the nature of the health condition under evaluation?	N/A	The economic evaluation was based on data from a single clinical study (multi-centre randomised controlled trial) and did not extrapolate treatment outcomes or costs beyond the study context or follow-up period.
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Partly	The time horizon (3 months) is arguably too short to capture all important differences in costs and outcomes. However, whilst it may be argued that comprehensive evaluation of these two types of surgery would require a longer follow-up, the focus of this economic evaluation is placed on investigating

		differences in perioperative costs and outcomes, including short-term (30 day) re-operation rates for disease recurrence, which is a similar focus to that of the corresponding Cochrane review.
Are all important and relevant health outcomes included?	Yes	Health outcomes assessed in the economic evaluation were: quality of life, measured by the SF-36 and Gastro-Intestinal Quality of Life Index; operating times; length of hospital stay; postoperative pain; morphine requirements; time to returning to a normal diet; and complications and readmissions 30 days post-surgery. The analysis therefore appears to include all important and relevant categories of major health outcomes that were assessed in the corresponding Cochrane review.
Are the estimates of baseline health outcomes from the best available source?	No	Estimates of baseline health outcomes are, in effect, derived from the control arm of the study, not using a systematic review. These estimates may or may not reflect baseline health outcomes in other populations of patients

		requiring surgical resection for ileocecal Crohn's disease.
Are the estimates of relative treatment effects from the best available source?	Partly	The authors utilised comparative effectiveness data collected from a single clinical study (multi-centre randomised controlled trial). This multi-centre randomised controlled trial is one of two trials included in the corresponding Cochrane review. The direction of estimates of relative treatment effects appear, in general, to be similar to those reported in the corresponding Cochrane review. The magnitude of estimates of relative treatment effects also appear, in general, to be similar to those reported in the corresponding Cochrane review. However, the analysis found a higher rate of wound infections amongst patients undergoing open surgery (6 of 30), compared with patients undergoing laparoscopic surgery (0 of 30); this is not consistent with the pooled estimate based on two trials, which found no significant difference in the rate of wound infections between

		groups.
Are all important and relevant costs included?	Unclear	A breakdown of resource use and unit costs is not provided, so it is unclear whether all appropriate costs were included.
Are the estimates of resource use from the best available source?	Unclear	The authors utilised resource use measures collected a single clinical study (multi-centre randomised controlled trial). it is unclear whether the estimates are similar in magnitude to the best available estimates, since quantities of resource use are not all reported separately from cost estimates and a breakdown of resource use is not provided. Operative time and hospital length of stay estimates are in the same direction as corresponding estimates reported in the Cochrane review.
Are the unit costs of resources from the best available source?	Partly	Unit costs were taken from one of the hospitals participating in the study, but are not reported separately form cost estimates.
Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Appropriate incremental results are presented for both costs and effects.

Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No sensitivity analyses were performed.
Is there no potential conflict of interest?	Unclear	The published report does not indicate whether or not there are financial conflicts of interest.
Overall assessment: Potentially serious limitations.		
Other comments: The study fails to meet one or more quality criteria and this could change the conclusions with respect to incremental costs and/or incremental effectiveness. See NHS EED structured abstract record for detailed commentary regarding potentially serious limitations of this study.		

Msika 2001

Study limitations (the level of methodological quality)	**Yes/ Partly /No/ Unclear/ NA**	**Comments**
Does the model structure adequately reflect the nature of the health condition under evaluation?	N/A	The economic evaluation was based on data from a single clinical study (non-randomised prospective cohort study) and did not extrapolate treatment outcomes or costs beyond the study context or follow-up period.
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Unclear	The time horizon for costs and outcomes is not explicitly stated.

		The authors state that "Mean follow-up time was 30 (2.6-53) and 10 (1.5-23) months in the OG [open surgery group] and LG [laparoscopic surgery group] respectively", but included health outcomes and costs all appear to be short-term. whilst it may be argued that comprehensive evaluation of these two types of surgery would require a longer follow-up, the focus of this economic evaluation is placed on investigating differences in perioperative costs and outcomes, which is a similar focus to that of the corresponding Cochrane review.
Are all important and relevant health outcomes included?	Partly	Clinical outcomes assessed in the economic evaluation were: conversion to open surgery; operating time; time to resolution of ileus; mortality; morbidity (perioperative and postoperative complications); and duration of hospital stay. The analysis therefore appears to include most important and relevant categories of major health outcomes that were assessed in

		the corresponding Cochrane review, with the exceptions of: re-operation rates for disease recurrence; blood loss; and postoperative pain.
Are the estimates of baseline health outcomes from the best available source?	No	Estimates of baseline health outcomes are, in effect, derived from the control arm of the study, not using a systematic review. These estimates may or may not reflect baseline health outcomes in other populations of patients requiring surgical resection for ileocecal Crohn's disease.
Are the estimates of relative treatment effects from the best available source?	No	The authors utilised comparative effectiveness data collected from a single clinical study (non-randomised prospective cohort study). It is difficult to assess the extent to which estimates of relative treatment effects used in the analysis are similar in magnitude to those estimated in the corresponding Cochrane review without undertaking further secondary analyses to compare these data with estimates reported in the Cochrane review. However, the direction of estimates of relative

		treatment effects appear, in general, to be similar to those reported in the corresponding Cochrane review, with the exception that this study found a statistically significant difference in duration of hospital stay between groups, favouring laparoscopy (the Cochrane review found no statistically significant difference between groups in length of stay). Also, no conversions to open surgery were performed in this study (the Cochrane review reports conversions in both groups, but no significant difference between groups).
Are all important and relevant costs included?	Unclear	A breakdown of resource use and unit costs comprising the estimated cost of hospital admission is not provided, so it is unclear whether all appropriate costs were included.
Are the estimates of resource use from the best available source?	Unclear / no	The authors utilised resource use measures collected a single clinical study (non-randomised prospective cohort study). It is unclear whether the estimates are similar in magnitude to the

		best available estimates, since quantities of resource use are not all reported separately from cost estimates and a breakdown of resource use is not provided. Estimated operative time is in the same direction as the corresponding estimate reported in the Cochrane review but estimated hospital length of stay is not (this study found a statistically significant difference in duration of hospital stay between groups, favouring laparoscopy, whilst the Cochrane review found no statistically significant difference between groups in length of stay). This may result in overestimation of the cost difference between groups in this study. The authors state that the two groups were comparable in terms of demographics, indications and procedures undertaken.
Are the unit costs of resources from the best available source?	Unclear	The authors state that: "Costs of hospitalization were determined according to reimbursement rates of the French National Health Care System." However,

		the source of unit costs is not cited and the price year used is not reported. In addition, the results are reported in US dollars (price year not stated) but no details of methods used to make adjustments for currency (and possibly price year) are reported. Unit costs are not reported separately from cost estimates.
Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Appropriate incremental results are presented for costs and effects.
Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No sensitivity analyses were performed.
Is there no potential conflict of interest?	Unclear	The published report does not indicate whether or not there are financial conflicts of interest.
Overall assessment: Potentially serious limitations.		
Other comments: The study fails to meet one or more quality criteria and this could change the conclusions with respect to incremental costs and/or incremental effectiveness. In particular, estimates of effects and resource use are derived from a non-randomised study, which is not as robust as a well-conducted (meta-analysis of) randomised controlled trial(s); the cost difference ('Cost of hospital admission') between open and laparoscopic patients may be overestimated; and the overall poor reporting makes it difficult to assess the reliability of results.		

Scarpa 2009

Study limitations (the level of methodological quality)	**Yes/ Partly /No/ Unclear/ NA**	**Comments**
Does the model structure adequately reflect the nature of the health condition under evaluation?	N/A	The economic evaluation was based on data from a single clinical study (non-randomised prospective cohort study) and did not extrapolate treatment outcomes or costs beyond the study context or follow-up period.
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Unclear	The time horizon for is not explicitly stated. However, all included costs appear to be short-term, probably to 3-months.
Are all important and relevant health outcomes included?	N/A	Economic evaluation is a cost-analysis.
Are the estimates of baseline health outcomes from the best available source?	N/A	Economic evaluation is a cost-analysis.
Are the estimates of relative treatment effects from the best available source?	N/A	Economic evaluation is a cost-analysis.
Are all important and relevant costs included?	Unclear	The cost categories comprising the measure of 'overall costs' are reported as: "the cost of the hospital stay, the cost of the instruments necessary for the operation and the cost of the lost

		working days during sick leave." Since a full breakdown of resource use and unit costs is not provided, it is unclear which cost items are included in the measure of 'the cost of the hospital stay', and it is therefore unclear whether or not all important and relevant resource use and costs were included given the perspective and the research question under consideration.
Are the estimates of resource use from the best available source?	Unclear / no	The authors utilised resource use measures collected a single clinical study (non-randomised prospective cohort study). It is unclear whether the estimates are similar in magnitude to the best available estimates, since quantities of resource use are not reported separately from cost estimates and a full breakdown of resource use is not provided.
Are the unit costs of resources from the best available source?	Yes	The authors state that: "The median cost of the hospital stay were based on [unit cost] estimates of standard charges in an Italian setting (North-Eastern Italy)…The social cost of lost

		working days was calculated based on standard Italian daily wages according to different jobs. Patients were asked about their job and their mean monthly income were retrieved from Italian Ministry of Work database; housewives, retired patients and students were considered to have no income." Whilst the sources of these unit cost data are not cited, the price year used (2008 Euros) is stated. Therefore, it appears that resources have been valued using up-to-date prices relevant to the study setting,
Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Appropriate incremental results are presented for costs.
Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No sensitivity analyses were performed.
Is there no potential conflict of interest?	Yes	The published report does not indicate any financial conflicts of interest.
Overall assessment: Potentially serious limitations.		
Other comments: The study fails to meet one or more quality criteria and this could change the conclusions with respect to incremental costs. In particular, estimates of resource use are derived from a non-randomised study, which is not as robust as a well-conducted (meta-analysis of) randomised controlled trial(s).		

Shore 2003

Study limitations (the level of methodological quality)	**Yes/ Partly /No/ Unclear/ NA**	**Comments**
Does the model structure adequately reflect the nature of the health condition under evaluation?	N/A	The economic evaluation was based on data from a single clinical study (non-randomised retrospective cohort study) and did not extrapolate treatment outcomes or costs beyond the study context or follow-up period.
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Unclear	The time horizon for costs and outcomes is not explicitly stated. The authors state only that "All patients were followed up 1 week after discharge and then at 3- and 6-month intervals." And that "Mean follow-up was 17.2 months in group A [laparoscopic] and 18.7 months in group B [open] without symptomatic clinical recurrence." Whilst it may be argued that comprehensive evaluation of these two types of

		surgery would require a longer follow-up, the focus of this economic evaluation is placed on investigating differences in perioperative costs and outcomes, which is a similar focus to that of the corresponding Cochrane review.
Are all important and relevant health outcomes included?	Partly	Clinical outcomes assessed in the economic evaluation were: conversion to open surgery; operating time; size of incision; number of trocars used; blood loss; time to resolution of ileus; mortality; morbidity (perioperative and postoperative complications; re-operations at 30 days); and duration of hospital stay. The analysis therefore appears to include most important and relevant categories of major health outcomes that were assessed in the corresponding Cochrane review, with the exception of post-operative pain. Another possible exception is 're-operation within 30 days', but this may have been considered as a type of 'morbidity' (it is not

		possible to ascertain this based on the published report, since no cases of morbidity were found in this series of patients).
Are the estimates of baseline health outcomes from the best available source?	No	Estimates of baseline health outcomes are, in effect, derived from the control arm of the study, not using a systematic review. These estimates may or may not reflect baseline health outcomes in other populations of patients requiring surgical resection for ileocecal Crohn's disease.
Are the estimates of relative treatment effects from the best available source?	No	The authors utilised comparative effectiveness data collected from a single clinical study (non-randomised retrospective cohort study). It is difficult to assess the extent to which estimates of relative treatment effects used in the analysis are similar in magnitude to those estimated in the corresponding Cochrane review without undertaking further secondary analyses to compare these data with estimates reported in the Cochrane review. However, the direction of estimates of relative treatment effects appear, in

		general, to be similar to those reported in the corresponding Cochrane review.
Are all important and relevant costs included?	Unclear	The economic evaluation assesses hospital charges only. A breakdown of resource use and unit costs comprising the estimated hospital charges is not provided, so it is unclear whether all appropriate costs (resource use items) were included.
Are the estimates of resource use from the best available source?	Unclear / no	The authors utilised resource use measures collected a single clinical study (non-randomised retrospective cohort study). It is unclear whether the estimates are similar in magnitude to the best available estimates, since quantities of resource use are not all reported separately from cost estimates and a breakdown of resource use is not provided. Estimated operative time is in the same direction as the corresponding estimate reported in the Cochrane review but estimated hospital length of stay is not (this study found a statistically significant difference in duration of hospital stay

		between groups, favouring laparoscopy, whilst the Cochrane review found no statistically significant difference between groups in length of stay). This may result in overestimation of the difference in hospital charges between groups in this study. The authors state that there were no statistically significant differences between the two groups in terms of baseline demographic or clinical characteristics.
Are the unit costs of resources from the best available source?	Yes	Hospital charges data were collected from patients' medical records, which indicates unit costs (hospital charges) were obtained from up-to-date sources relevant to the study setting.
Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Appropriate incremental results are presented for costs and outcomes.
Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No sensitivity analyses were performed.
Is there no potential conflict of interest?	Unclear	The published report does not indicate whether or not there are financial conflicts of interest.

Overall assessment: Potentially serious limitations.
Other comments: The study fails to meet one or more quality criteria and this could change the conclusions with respect to incremental costs and/or incremental effectiveness. In particular, estimates of effects and resource use are derived from a non-randomised study, which is not as robust as a well-conducted (meta-analysis of) randomised controlled trial(s); and the difference in hospital charges between open and laparoscopic patients may be overestimated.

Young-Fadok 2001

Study limitations (the level of methodological quality)	**Yes/ Partly /No/ Unclear/ NA**	**Comments**
Does the model structure adequately reflect the nature of the health condition under evaluation?	N/A	The economic evaluation was based on data from a single clinical study (non-randomised case-control study using matched patient pairs) and did not extrapolate treatment outcomes or costs beyond the study context or follow-up period.
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Unclear	The time horizon for costs and outcomes is not explicitly stated. However, all included costs appear to be short-term. Whilst it may be argued that comprehensive evaluation of these two types of surgery would

		require a longer follow-up, the focus of this economic evaluation is placed on investigating differences in perioperative costs and outcomes, which is a similar focus to that of the corresponding Cochrane review.
Are all important and relevant health outcomes included?	Partly	Clinical outcomes assessed in the economic evaluation were: the number of days to clear liquids; the number of days to a regular diet; narcotic use; operating time; anesthesia time; confirmation of pathology; intraoperative complications; postoperative complications; conversion rate (laparoscopic group); and hospital length of stay. The analysis therefore appears to include most important and relevant categories of major health outcomes that were assessed in the corresponding Cochrane review, with the exceptions of intra-operative blood loss and post-operative pain.
Are the estimates of baseline health outcomes from the best available source?	No	Estimates of baseline health outcomes are, in effect, derived from the control arm of the study,

		not using a systematic review. These estimates may or may not reflect baseline health outcomes in other populations of patients requiring surgical resection for ileocecal Crohn's disease.
Are the estimates of relative treatment effects from the best available source?	No	The authors utilised comparative effectiveness data collected from a single clinical study (non-randomised case-control study using matched patient pairs). It is difficult to assess the extent to which estimates of relative treatment effects used in the analysis are similar in magnitude to those estimated in the corresponding Cochrane review without undertaking further secondary analyses to compare these data with estimates reported in the Cochrane review. However, with respect to operative time, the direction of the estimate of relative treatment effects appears to be similar to that reported in the corresponding Cochrane review.
Are all important and relevant costs included?	Yes	All important and relevant resource use and costs appear to be included given the perspective

		and the research question under consideration.
Are the estimates of resource use from the best available source?	Unclear / no	The authors utilised resource use measures collected a single clinical study (non-randomised case-control study using matched patient pairs). It is unclear whether the estimates are similar in magnitude to the best available estimates, since quantities of resource use are not reported separately from cost estimates and a breakdown of resource use is not provided. Estimated operative time is in the same direction as the corresponding estimate reported in the Cochrane review but estimated hospital length of stay is not (this study found a statistically significant difference in duration of hospital stay between groups, favouring laparoscopy, whilst the Cochrane review found no statistically significant difference between groups in length of stay). This may result in overestimation of the difference in hospital charges between groups in this study.

Are the unit costs of resources from the best available source?	Yes	Cost data appear to have been obtained from up-to-date sources relevant to the study setting.
Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	Appropriate incremental results are presented for costs and outcomes.
Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No sensitivity analyses were performed.
Is there no potential conflict of interest?	Unclear	The published report does not indicate whether or not there are financial conflicts of interest.
Overall assessment: Potentially serious limitations.		
Other comments: The study fails to meet one or more quality criteria and this could change the conclusions with respect to incremental costs and/or incremental effectiveness. In particular, estimates of effects and resource use are derived from a non-randomised study, which is not as robust as a well-conducted (meta-analysis of) randomised controlled trial(s); and the difference in hospital charges between open and laparoscopic patients may be overestimated.		

Wildschut 2011

Ngai 2000

Study limitations (the level of methodological quality)	**Yes/ Partly /No/ Unclear/ NA**	**Comments**
Does the model structure adequately reflect the nature of the health condition under evaluation?	N/A	The economic evaluation was based on data from a single clinical study (prospective, single centre randomised controlled trial) and did not extrapolate treatment outcomes or costs beyond the study context or follow-up period.
Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	The time horizon is not explicitly stated; however all costs and outcomes are short-term (encompassing the primary health outcome – percentage of women who aborted within 24 hours – and incidence of short-term side effects). The clinical outcomes considered in this economic evaluation are broadly consistent with those considered in the corresponding Cochrane review, which indicates the time horizon is sufficiently long to

		reflect all important differences in outcomes and associated costs.
Are all important and relevant health outcomes included?	Yes	Health outcomes assessed in the economic evaluation were: percentage of women who aborted within 24 hours; incidence of nausea; incidence of vomiting; incidence of dizziness; incidence of fatigue; incidence of lower abdominal pain; incidence of breast tenderness; incidence of diarrhoea; incidence of headache; and preferences for the regimens evaluated. Measurement of the primary health outcome - percentage of women who aborted within 24 hours – included recording of rates of suction evacuation for incomplete abortion and surgical treatment for failed abortion. The analysis therefore appears to include all important and relevant health outcomes that were assessed in the corresponding Cochrane review, with the exceptions of blood loss, uterine rupture and pain associated with surgical evacuation and/or surgical

		treatment for incomplete/failed abortion.
Are the estimates of baseline health outcomes from the best available source?	Partly	Estimates of baseline health outcomes are, in effect, derived from the control arm of the study, not using a systematic review. These estimates may or may not reflect baseline health outcomes in other patient populations referred for second trimester termination of pregnancy.
Are the estimates of relative treatment effects from the best available source?	Yes	The authors reported comparative effectiveness data collected from a single clinical study (prospective, single centre randomised controlled trial). The estimate of relative treatment effect for the primary clinical outcome reported in the analysis - percentage of women who aborted within 24 hours is - similar in direction magnitude to the pooled effect-size estimated in the corresponding Cochrane review, which pools data collected from three RCTs that administered different drug doses and regimens.
Are all important and relevant costs included?	No	The authors report only limited information regarding costs: the

		relative unit costs of the two drug regimens evaluated. The relative costs associated with management of incomplete abortions and side effects of treatment are not evaluated.
Are the estimates of resource use from the best available source?	N/A	The authors report only limited information regarding costs: the relative unit costs of the two drug regimens evaluated.
Are the unit costs of resources from the best available source?	Unclear	The source of the unit cost data is not stated.
Is an appropriate incremental analysis presented or can it be calculated from the data?	No	Appropriate incremental results are presented for effects, but no incremental results are presented with respect to costs, since the authors report only the relative unit costs of the two drug regimens evaluated.
Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	No	No sensitivity analyses were performed.
Is there no potential conflict of interest?	Unclear	The published report does not indicate whether or not there are financial conflicts of interest,
Overall assessment: Potentially serious limitations.		
Other comments: The study fails to meet one or more quality criteria and this could change the conclusions with respect to incremental costs. However, it is important to note that this study focused primarily on evaluating relative treatment effects; it did not set out to evaluate costs beyond reporting limited information regarding the relative unit costs of the two drug regimens evaluated in		

the study setting.

Komossa 2011

Beard 2006