



Economic evaluation alongside factorial trials: a systematic review of empirical studies

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Table 1: Search strategies used

DATABASE SEARCHED	TIMESPAN	SEARCH STRATEGY
NHS EED	All years	(economic evaluation*) and (factorial design*)
Embase	1974 to 2013 July 30	1. "cost"/ or cost-utility analysis.mp. or "cost benefit analysis"/ or "health care cost"/ or "quality of life"/ (442989) 2. cost-effective\$.mp. (140957) 3. economic evaluation\$.mp. (13687) 4. 1 or 2 or 3 (544342) 5. factorial design\$.mp. (1111) 6. 4 and 5 (39)
EconLit	All years	S1 economic evaluation* S2 cost-utility analysis S3 cost-benefit analysis S4 cost-effective* S5 S1 OR S2 OR S3 OR S4 S6 factorial design* S7 S5 AND S6
COCHRANE	All years	#1 economic evaluation* #2 factorial trial* #3 #1 and #2
Science Citation Index (Expanded)	All years	(Factorial trial*) and (economic evaluation*)
Conference proceedings citation	All years	(Factorial trial*) and (economic evaluation*)
Ovid MEDLINE(R)	1946 to July Week 3 2013	1. Quality-Adjusted Life Years/ or Cost-Benefit Analysis/ or Health Care Costs/

		or cost-utility analysis.mp. or "Quality of Life"/ (194798) 2. cost-effective\$.mp. (70146) 3. economic evaluation\$.mp. (6062) 4. 1 or 2 or 3 (236930) 5. factorial design\$.mp. (961) 6. 4 and 5 (30)
BioMed Central	All years	(Factorial trial*) and (economic evaluation*)

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Table 2: Summary of the studies used in the review

	AUTHOR(S) AND YEAR OF PUBLICATION	TYPE OF FACTORIAL TRIAL	TIME HORIZON OF THE RESEARCH	OBJECTIVE(S) OF THE RESEARCH	TYPE OF ECONOMIC EVALUATION	PERSPECTIVE	SAMPLE SIZE	CONTROL GROUP USED	PRIMARY OUTCOME(S)	SENSITIVITY ANALYSIS UNDERTAKEN	METHOD OF ANALYSIS AND ITS APPROPRIATENESS TO THE RESEARCH OBJECTIVES	CONSIDERED INTERACTIONS IN ECONOMIC OUTCOMES
1	Dangour et al., 2011	2x2	Two (2) years.	The objective(s) of the research was to assess the effectiveness and cost-effectiveness of the Chilean national nutritional supplementation program on decreasing the incidence of pneumonia and a training exercise program to increase walking capacity in older people in Santiago Chile.	Cost-effectiveness analysis.	Societal	2799	Usual care	Cost/unit effect	Not stated.	At-the-margins analysis	No
2	The UK BEAM trial team, 2004	2x2	One (1) year	The objective of the research was to assess the cost-effectiveness of adding spinal manipulation, exercise or a combination of the treatments to "best care" for patients	Cost-utility analysis	Health service	1287	placebo	cost/QALY	One-way sensitivity analysis for three different scenarios.	Within-the-table analysis	Yes

				consulting with low back pain.								
3	Barton et al., 2009	2x2	Two (2) years	The objective of the research was to estimate the cost-effectiveness of four different lifestyle interventions for knee pain	Cost-utility analysis	Health service	389	Usual care	Cost/QALY	Probabilistic-sensitivity analysis.	Within-the-table analysis.	No
4	Jafar et al., 2011	2x2	Two (2) years	The objective of the research was to assess the cost-effectiveness of Home Health Education (HHE) and/special training of GPs on the blood pressure levels of adults aged 40yrs or above with hypertension	Cost-utility analysis	Societal	1341	placebo	cost/DALY	Probabilistic sensitivity analysis	Within-the-table analysis	No
5	Pinto et al., 2013	2x2	One (1) year	The objective of the trial was to evaluate the cost-effectiveness of manual physiotherapy, exercise physiotherapy	Cost-utility analysis.	Health service and societal	206	placebo	Cost/QALY	One-way sensitivity analysis	Within-the-table analysis	No

				and a combination of the two for patients with osteoarthritis of the hip or knee								
6	Morris et al., 2011	2x2	One (1) year	The objective of the research was to assess the cost effectiveness of a rehabilitation program and educational booklet each compared with usual care for the post-operative management of patients undergoing surgery	Cost-utility analysis	Health service and societal	338	placebo	cost/QALY	nonparametric bootstrapping	At-the-margins analysis	No
7	Thomas et al., 2005	2x2	Two (2) years	The objective was to compare the cost-effectiveness of exercise and monthly telephone support for the treatment of knee pain.	Cost-effectiveness analysis	Health service perspective	786	Usual care	Cost/unit effect	nonparametric bootstrapping	At-the-margins analysis	No
8	Campbell et al., 2005	2x2	One (1) year	To assess the efficacy and cost-effectiveness of a home safety program and a home exercise	Cost-effectiveness analysis	societal	391	Usual care	Cost/unit effect	one-way sensitivity analysis	At-the-margins analysis	No

				program to reduce falls and injuries in older people with low vision.									
9	Lindgren et al., 2009	2x2	Three (3) years	To assess the cost effectiveness of four alternative treatment strategies in patients with hypertension and three or more cardiovascular risk factors in the UK	Cost-utility analysis	Health service and societal perspectives	19,257	Usual care	Cost/QALY	One-way sensitivity analysis and probabilistic sensitivity analysis	Within-the table analysis	No	
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21	10	Effing et al., 2009	2x2	One (1) year	To assess the Cost-effectiveness of self-treatment of exacerbations on the severity of exacerbations in patients with COPD	Cost-effectiveness analysis	Health service	142	Usual care	Cost/unit effect	Probabilistic sensitivity analysis	At-the-margins	No
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30	11	Lewca et al., 2013	2x2	Five (5) years	To assess the Effects and cost-effectiveness of community mobilisation through women's groups, and health education through female volunteer peer counsellors on	Cost-effectiveness analysis	Health service	185888	placebo	Cost/unit effect	Not stated	Within-the-table analysis	No
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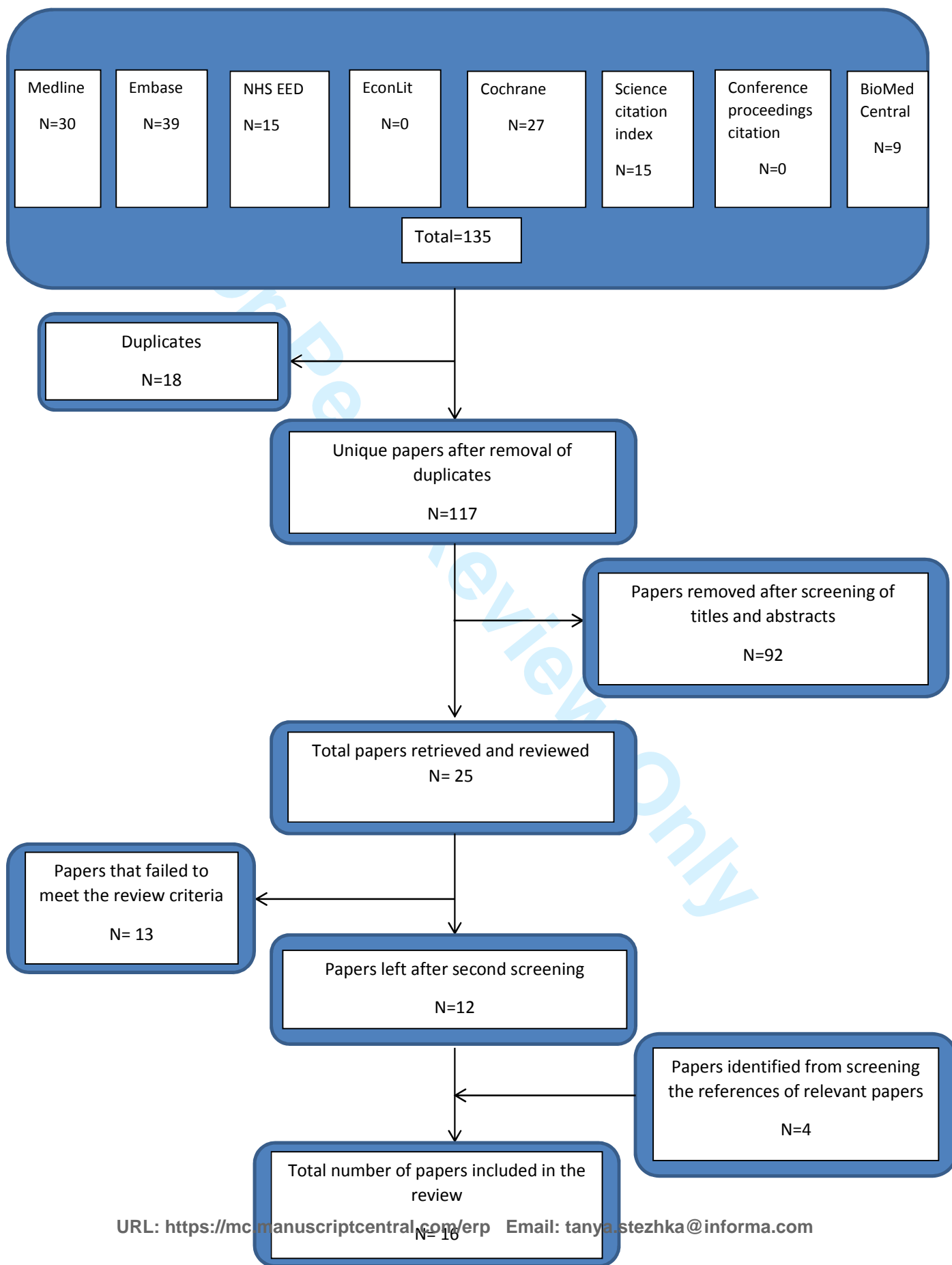
				rates of infant care, feeding, morbidity, and mortality.								
1 2	Hollinghurst et al., 2008	4x2	One (1) year	An economic evaluation of therapeutic massage, exercise, and lessons in the Alexander technique for treating persistent back pain	Cost-utility analysis and cost-consequence analysis	Health service, societal and patient	579	Usual care	Cost/QALY	One-way sensitivity analysis and non-parametric bootstrapping	Within-the-table analysis	No
1 3	Bakkhai et al., 2003	2x2	One (1) year	To assess the Cost-Effectiveness of Coronary Stenting and Abciximab for Patients With Acute Myocardial Infarction	Cost-utility analysis	Health service	1703	Usual care	Cost/QALY	Non-parametric bootstrapping	Within-the-table analysis	No
1 4	Boyle et al., 2007	2x2	One (1) year	To assess the effect and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment	Cost-effectiveness analysis	patient	161	Usual care	Cost/unit effect	Non-parametric bootstrapping	Within-the-table analysis	No
1 5	McBeth et al., 2012	2x2	One (1) year	To assess the cost-effectiveness of cognitive behaviour therapy, Exercise,	Cost-utility analysis	Health service	442	Usual care	Cost/QALY	Non-parametric bootstrapping	Within-the-table analysis	No

				or both for treating chronic widespread pain								
1 6	Waterhouse et al., 2010	2x2	One (1) year	To assess the cost-effectiveness of community versus hospital pulmonary rehabilitation for chronic obstructive pulmonary disease followed by telephone or conventional follow-up	Cost-utility analysis	Health service	240	Usual care	Cost/QALY	Non-parametric bootstrapping	Within-the-table analysis	No

Table 3: Summary of the main differences between the at-the-margins approach and the within-the-table approach

Within-the-table approach	At-the-margins approach
All interventions within the trial are treated separately. E.g. in a 2x2 trial comparing interventions A, B, AB and O all arms are treated separately	Considers the trial as separate overlapping trials. E.g. in a 2x2 trial comparing A,B,AB and O, all participants who received A (i.e. A and AB) are compared to those who did not receive A (i.e. B and O)
Takes interactions between interventions into account (i.e. assumes that the effects of intervention A are influenced by the inclusion of intervention B and vice versa)	Assumes independence of interventions (i.e. the effects of intervention A are not influenced by the inclusion of intervention B and vice versa)
The approach is less efficient (i.e. effects of treatments are not based on the entire sample size)	The approach is more efficient (i.e. treatment effects are based on the entire sample size)
Estimates obtained are considered to be unbiased	Estimates obtained are considered to be biased if interactions are present

Figure 1: Summary of the search strategy



US English, ERP October, Review, 1 figure, 3 tables

Economic evaluation alongside factorial trials: a systematic review of empirical studies

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ABSTRACT

Although economic evaluations have been carried out alongside factorial trials, there seems to be limited guidance/consensus on appropriate methods of analysis. Following Centre for Review and Dissemination guidance, a systematic review of published literature for all years was carried out to explore how economic evaluation alongside factorial trials have been conducted and only full economic evaluations conducted alongside factorial trials were included. A total of 16 relevant studies were identified and an assessment of these indicated that two methods: within-the-table and at-the-margins approaches were used for the analysis. With the exception of one study, all others did not consider interactions in costs and outcomes or give a detailed explanation of why a particular approach was adopted. The authors recommend that additional guidance is needed and further research is required to evaluate the impact of alternative methods on policy recommendations and establish good practice methods for the economic analysis of factorial trials.

Key words: cost-benefit analysis, cost-effectiveness, cost-utility analysis, economic evaluation, factorial design, factorial trial.

INTRODUCTION

Health economic evaluations are commonly used to inform resource allocation decisions in most industrialised nations and many funding bodies such as the UK National Institute for Health Research's Health Technology Assessment Programme now routinely request the assessment of cost-effectiveness to be 'piggybacked' on Randomised Controlled Trials (RCT's) [1-3]. While there are several types of RCT's used in medical research, factorial trials are becoming more prevalent in a context where health care research budgets are increasingly constrained.

Factorial trials "*test the effects of two or more interventions simultaneously using various combinations of the interventions within the same trial*" [4]. There are several factorial designs, with the most common being the 2x2 which assesses two interventions with each one of them having two levels. For example, in a 2x2 factorial trial of self-management options for hand osteoarthritis, patients can be randomised to either of the following interventions: usual care, joint protection, hand exercises or a combined intervention (joint protection plus hand exercises). This allows for more information to be obtained in a single trial at a reduced overall cost [5]. In addition, factorial trials allow for the investigation of interactions between the treatments under scrutiny [6-7], and in the absence of interactions, they provide greater power than traditional multiple-arm trials of similar sample size evaluating the same interventions [8].

As a consequence, there is now a growing interest in employing these designs in trial-based economic evaluations [9]. However, unlike in the analysis of clinical outcomes, where the methods of analysis are well established, methods for the economic analysis of factorial trials remain unclear [10, 11].

Recent research suggested that the appropriate analysis of factorial designs in economic evaluations is important, not only because interactions are more likely to occur in economic data but also because economic evaluations focus on the estimation of incremental cost-effectiveness ratios (ICERs) as opposed to hypothesis testing which is the main focus of clinical studies [10]. There is therefore a greater potential for bias which can affect the validity of results if the analysis is not carried out appropriately. In addition, this type of trial leads to a reduction in sample size if interactions are accounted for. This is problematic because most two arm trials are known to be underpowered for the

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3 economic analysis and as a consequence, the factorial trial could potentially lead to further uncertainty
4 in economic outcomes [11]. Even though these challenges have been identified, there is still
5 uncertainty about how to overcome them.
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9 The objective of this study is to systematically review economic evaluations conducted alongside
10 factorial trials with the aim of exploring the empirical methods involved and to offer
11 recommendations that could potentially assist in the development of good practice guidelines in this
12 context. To the best of our knowledge, no other study has conducted a systematic review of economic
13 evaluations alongside factorial trials.
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19 20 21 **METHODS**

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23 A systematic review of economic evaluations alongside factorial trials was conducted following the
24 guidelines outlined by the UK Centre for Review and Dissemination (CRD) [12]. In the absence of
25 Medical Subject Heading (MeSH) for factorial trials and economic evaluations, search terms,
26 including truncation where appropriate, included the terms “cost-benefit analysis”, “cost-effectiveness
27 analysis”, “cost-utility analysis”, “economic evaluation”, “factorial design” and “factorial trial”. The
28 following electronic databases were searched for relevant studies published for all years: CENTRAL
29 (Cochrane Wiley), MEDLINE (Ovid), EMBASE (Ovid), EconLit (EBSCO), NHS EED (Cochrane
30 Wiley), Science Citation Index (ISI) and Conference Proceedings Citation Index (ISI). In addition to
31 this, a methodological research in the Cochrane Methodology database (Cochrane Wiley) and BioMed
32 Central portfolio of journals was also conducted. The final search strategies across the different
33 databases are detailed in Table 1.
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46 To be included in the review, studies had to be full economic evaluations conducted alongside a
47 factorial trial. Studies were excluded if they were partial or non-economic evaluation studies, cohort
48 studies, case-control studies, systematic reviews, study protocols or commentaries. Non-English
49 studies and grey literature were also excluded.
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55 Literature search was carried out between July and August 2013 in two stages. First, titles and
56 abstracts were screened to identify potentially relevant papers. The second stage involved screening
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3 the full papers considered to be potentially relevant. The screening process in both stages was done
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5 against the inclusion and exclusion criteria. The reference lists of the papers identified after the
6
7 second screening process were also screened for additional relevant papers. A quality assessment was
8
9 not conducted because the focus of the review was to explore the methodologies that have been
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11 employed in practise for the economic analysis of factorial trials and not the validity of the estimates
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13 obtained from the included studies. Thus, all the relevant studies identified from the selection process
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15 were subsequently considered for data extraction. For each of the studies included in the review, data
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17 were extracted concerning the perspective of the study and type of economic evaluation, cost and
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19 outcomes considered and method of analysis of factorial trials.
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21 22 **RESULTS**

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24 The electronic database search identified 135 potentially relevant papers of which 18 were duplicates.
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26 Out of the 117 remaining papers, 92 were excluded after the screening of titles. A thorough
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28 assessment of the 25 papers identified to be potentially relevant led to the exclusion of a further 13
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30 papers from the list, limiting the number of papers to 12. The 13 papers were excluded for the
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32 following reasons; 7 of them were study protocols, 3 were systematic reviews and 3 were not full
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34 economic evaluations. The reference lists of the 12 relevant papers were also screened and this led to
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36 the identification of 4 additional papers. A total of 16 papers were therefore included in the review.
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38 Figure 1 shows a flow chart of the papers identified, retrieved and retained or excluded at each stage
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40 of the review process.
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43 44 **Summary of selected studies**

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46 As shown in table 2, the studies included in the review were published between 2003 and 2013. Of
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48 these, 15 were '2x2' trials and one was a '4x2' trial. The included studies were conducted across
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50 eight different countries: Chile [13], the UK [14-21], New Zealand [22, 23], Pakistan [24], Sweden
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52 [25], Netherlands [26], Malawi [27] and the USA [28]. Most studies were related to musculoskeletal
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54 disease (seven studies) or cardiovascular disease (five studies).
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Perspectives and type of economic evaluation undertaken

Studies were conducted from either a societal [13,23,24], a health service [14,15,17,20,21,26,27,28], or patient perspective [19]. Three studies considered both a health service and societal perspective [16,22,25] and one considered all three [18]. In all the studies, the reason for adopting a particular perspective was given and this was appropriately followed for collecting the right cost data within the boundaries of the perspective adopted.

Two types of economic evaluations were mainly undertaken across the sixteen studies. These are cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) (Table 2). CEA was undertaken in six studies, [13,17,19,23,26,27] whereas CUA was undertaken in nine studies, [14-16,20-22,24,25,28] with one study undertaking both cost-consequence and cost-utility analysis [18]. All studies gave a justification of why they employed each economic evaluation technique and it was found to be appropriate to the research objectives. The sample size of most studies (approximately 63%) was less than 800 participants. Only two studies recruited more than 3000 participants. The sample sizes were calculated to detect the clinical effects in all studies. Studies differed in terms of what constituted the control group for their research. Eleven studies [13,15,17-21,23,25,26,28] used 'usual care' as the control group whereas five studies [14,16,22,24,27] used a placebo.

Costs and outcomes

Six studies had their primary outcome of interest reported in cost per unit effect [13,17,19,23,26,27] whereas ten studies reported their primary outcomes in cost per Quality Adjusted Life Year (QALY) gained [14-16,18,20-22,25,28] or cost per Disability Adjusted Life Year (DALY) averted [24]. In terms of costing, all the studies adopted the ingredient approach (where estimates of total resource use are multiplied by their respective unit prices) to estimate the cost of the interventions. In all studies where the trials were conducted over a time horizon of one year, cost and QALYs were not discounted whereas in studies with larger time horizon costs and QALYs were discounted.

Analytical approaches to the economic analysis of factorial trials

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3 Although not explicitly stated, two methods of analysis were identified across the studies; within-the-
4 table approach [14-15,18-20,22,24,25,27,28] and at-the-margins approach [13,16,17,23,26]. The
5 within-the-table approach implicitly assumes that the interventions within the factorial design are
6 mutually exclusive and therefore considers each of them as a separate treatment strategy allowing the
7 effect of interactions to be easily seen [29]. The at-the-margins approach implicitly assumes that the
8 interventions under investigation are independent and there is no interaction between treatments. The
9 trial is therefore analysed as though it were overlapping arms of an RCT comparing the effects of
10 treatments separately [29]. One study considered both methods and stated that the reason for
11 employing both methods was to provide the most relevant information for policy makers (within-the-
12 table approach) and to carry out the analysis in line with the convention for a factorial design (at-the-
13 margins approach) [18]. A summary of the characteristics of both approaches are presented in table 3.
14 It should be noted that apart from the choice of approach in the clinical study and the objective of the
15 economic analysis, other factors such as sample size, disease area or comparator did not seem to have
16 an influence on the choice of approach.
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32 A thorough assessment of the studies reviewed indicated that, none of the studies tested interactions
33 between treatments in terms of costs and outcomes nor gave a detailed explanation on how they were
34 going to account for the factorial nature of the trial. The only instance where reference was made to
35 interaction in cost was the study by The UK BEAM trial team [14], where they mentioned a
36 comparison of four distinct treatments although cost showed no interaction between treatments. In all
37 other instances where studies mentioned an interaction was to reiterate whether any statistically
38 significant interaction was evident in clinical outcomes, which then informed the decision about
39 which method of analysis to adopt rather than testing for interactions in the economic outcomes.
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49 **DISCUSSION**

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51 The literature search indicated that two methods (within-the-table and at-the-margins approach) are
52 commonly used in the economic analysis of factorial trials. The choice of method was found to be
53 mainly influenced by the method adopted in the clinical study. It is therefore apparent that for some of
54 the studies, even though the clinical trial detected interactions, if the objective was to calculate the
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3 separate ICERs for the factors, at-the-margins approach was employed instead of the within-the-table
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5 approach and vice-versa [14].
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8 None of the studies explored interactions between economic outcomes or stated the reasons why such
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10 interactions were not expected to occur. This is problematic as economic outcomes are different from
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12 the clinical ones, and thus special considerations should be given to their analysis. This may be due to
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14 a lack of clear guidance on how economic evaluations alongside factorial trials should be conducted
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16 and their methodological challenges.
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19 One such challenge may relate to the sample size of the trial. In all studies, sample sizes used were
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21 calculated with the purpose of detecting the clinical effects of the interventions under scrutiny. The
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23 problem that arises here is that some trials may be inadequately powered to detect plausible clinical
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25 interactions [7,30], and thus the absence of proof of evidence for interactions is equated to proof of
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27 absence of evidence for interactions in the clinical outcomes [30]. Given that interactions are more
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29 likely to occur in economic outcomes rather than the clinical [10] this assumption is likely to be
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31 invalid. Even when interactions in economic outcomes are identified, conducting the appropriate
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33 analysis within-the-table may result in further loss of power and greater uncertainty to the economic
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35 results.
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38 It is also worth stating that, unlike clinical outcomes that are generally normally distributed, economic
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40 outcomes generally follow a skewed distribution and are associated with a higher variance, which
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42 impact on the way they should be analysed [31,32]. Therefore, even if the trial is adequately powered
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44 to detect the main difference in clinical outcome, it will be typically underpowered for the analysis of
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46 economic outcomes. But as can be seen from the sample sizes employed in the various trials, the issue
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48 of sample size in relation to the detection of interactions (in economic outcomes) and the use of
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50 appropriate sample size in relation to the distribution of the economic outcomes for their effective
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52 analysis were not appropriately taken into consideration by almost all the studies.
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55 Only one study [18] employed both the at-the-margins and within-the-table approaches, and even
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57 though this study, like the rest, did not give an explicit explanation of how the factorial nature of the
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3 trial was accounted for when the economic variables were analysed, it may be argued that presenting
4 both analyses is more informative, even when they result in contradicting recommendations. In terms
5 of economic evaluation in general, there were consistencies with respect to the methodological and
6 practical aspects. These consistencies can be attributed to the immense literature and guidelines
7 available for methodologically robust economic evaluations. Hence researchers have a clear
8 understanding and direction on how economic evaluations should be conducted and in most cases, if
9 not all, follow it accordingly [33-37].
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13 To the best of our knowledge, this is the first study to review economic evaluations conducted
14 alongside factorial trials and therefore provides a description of the current state of play in the
15 economic analysis of factorial trials. A possible limitation is the broad nature of the research question.
16 This study was not limited to a particular disease area and it is quite possible that some studies might
17 have been missed out. However, we made every effort to identify all relevant studies by developing
18 the search strategy with advice from an information specialist.
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22 The increasing pressures on health care and research budgets are likely to be associated with an
23 increase in the use of factorial trials. This study highlighted the inconsistent use of methods in the
24 health economic analysis of factorial trials. Few studies have compared methods for the analysis of
25 factorial trials. One study found that the different methods led to different conclusions [9], whilst the
26 other found that choice of method did affect the conclusions of the study. However, the degree to
27 which the intervention was considered cost-effective varied with the different approach i.e. the
28 probability of the intervention being cost-effective differed with the various approaches [11].
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32 Further research is still required in order to evaluate the impact of alternative methods on policy
33 recommendations and establish good practice guidelines on the design and economic analysis of
34 factorial trials. Until a consensus is reached with respect to the economic analysis of factorial trials, it
35 is suggested that researchers should test for interactions in economic outcomes before deciding on the
36 primary analysis and explore alternative approaches in a secondary analysis. This can be achieved by
37 using a regression approach, which can easily be adapted to take the form of a within-the-table or at-
38 the-margins approach by either including or excluding an interaction term in the regression model
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3 [29]. When such interactions are unlikely to appear, the reasons should be explicitly stated. Such an
4 approach will potentially ensure that the economic and other benefits of factorial trials are not
5 translated into suboptimal policy recommendations.
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8 9 10 **EXPERT COMMENTARY**

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12 In an increasingly resource constrained environment, there is growing interest in employing factorial
13 designs, which assess two or more interventions simultaneously using various combinations of the
14 interventions within the same trial. Although methods for the analysis of clinical endpoints alongside
15 factorial trials are well established, there is limited methodological guidance for the economic
16 analysis. Most published economic evaluations assume no interaction between interventions and are
17 inconsistently reported. Overlooking potential interactions on cost and outcome data may introduce
18 bias and result in suboptimal policy recommendations. Further work is required to evaluate the impact
19 of alternative methods on results from cost-effectiveness analyses alongside factorial trials.
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28 29 30 **FIVE YEAR VIEW**

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32 The increasing pressures on health care and research budgets are likely to be associated with an
33 increase in the use of factorial trials and a corresponding increase in economic evaluations conducted
34 along such trials. With the limited guidance available, it is expected that the inconsistent use of
35 methods in the health economic analysis of factorial trials will continue. However, with the
36 publication of additional studies highlighting the issues surrounding the economic analysis of factorial
37 trials and the potential policy implications, there would be an increased awareness amongst
38 researchers. We expect to see more research comparing alternative analytical approaches and hope that
39 this would lead to an increase in the development of methods and guidance for the economic analysis
40 of factorial trials over the next five years.
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56 57 58 **KEY ISSUES**

- There is a growing interest by health economists in employing factorial trials when analysing economic data in trial-based economic evaluations. However, methods for the economic analysis of factorial trials remain unclear and there seems to be limited guidance on which method is the most appropriate and under which circumstances.
- The results from this study showed that two different methods: ‘within-the-table’ and ‘at-the-margins’ approaches were used for the analysis. However, with the exception of one study, all others did not consider interactions in costs and outcomes or give a detailed explanation of why a particular approach was adopted.
- This review found that although there was consistency in the application of general principles for conducting economic evaluations, there was lack of agreement with respect to methods for the economic analysis of factorial trials.
- Further research is required in order to evaluate the impact of alternative methods on policy recommendations and establish good practice methods on the design and economic analysis of factorial trials.

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