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The reporting of treatment non-adherence and its associated impact on economic evaluations conducted alongside randomised trials: a systematic review

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Abstract

Objectives: To review trial-based economic evaluations, identifying: 1) the proportion reporting adherence; 2) methods for assigning intervention costs according to adherence; 3) which participants were included in the economic analysis; and 4) statistical methods to estimate cost-effectiveness in those who adhered. We provide recommendations on handling non-adherence in economic evaluations.

Methods: The NHS Economic Evaluation Database was searched for recently published trials. We extracted information on the methods used to assign shared costs in the presence of non-adherence and methods to account for non-adherence in the economic analysis.

Results: Ninety-six eligible trials were identified. For one-off interventions, 86% reported the number of participants initiating treatment. For recurring interventions, 56% and 73% respectively reported the number initiating and completing treatment, whilst 66% reported treatment intensity. Most studies (23/31 [74%] trials and 42/53 [79%] trials of one off and recurring interventions respectively) reported strict intention to treat or complete case analyses. A minority (3/31 [10%] and 7/53 [13%] respectively), however, performed a per protocol analysis. No studies used statistical methods to adjust for non-adherence directly in the economic evaluation. Only 13 studies described patient-level allocation of intervention costs; there was variation in how fixed costs were assigned according to adherence.

Conclusion. The majority of trials reported a measure of adherence, but reporting was not comprehensive. A non-trivial proportion of studies report a primary per protocol analysis which potentially produces biased results. Alongside primary ITT analysis, statistical methods for obtaining an unbiased estimate of cost-effectiveness in adherers should be considered.

Introduction

Treatment adherence has been defined as the degree of correspondence between a participant's intended treatment and their actual treatment [1]. Those who are unable to adhere to their allocated treatment, e.g. due to experiencing side effects, are more likely to have poorer clinical outcomes and may also have higher health care costs [2,3]. Randomised controlled trials (RCTs) are often considered the gold standard for assessing the cost-effectiveness of health care interventions. The prevalence of treatment non-adherence in RCTs, however, can be non-trivial [1]. Without clarity in reporting non-adherence and the methods used to accommodate it, the findings from a randomised trial may be difficult to interpret.

Recent reviews of RCTs have highlighted vague and incomplete reporting of adherence and inconsistency in how non-adherence was incorporated in the analysis [1,4]. Trial-based economic evaluations potentially suffer from similar shortfalls in reporting, however this has not previously been investigated as part of a systematic review. The Consolidated Standards of Reporting Trials (CONSORT) statement supports "intention-to-treat" (ITT) analyses which include all participants in the analysis group to which they were randomly allocated regardless of treatment adherence [5].The major benefit of ITT analysis is that it preserves randomisation and therefore eliminates selection bias in estimates of the treatment effect and cost-effectiveness. Because ITT analyses does not require adherence information, however, this may reduce the motivation for collecting and reporting adherence. Information on treatment adherence allows a more detailed exploration and understanding of the costs and effects of treatment. For example, adherence information can allow estimation of treatment cost-effectiveness in participants who adhere to the intervention, thereby informing policy makers in other settings where adherence is different from that of the RCT [6].

There has been little discussion about the unique challenges presented by non-adherence in trial-based economic evaluations. For example, shared (or overhead) costs might be allocated equally across all those randomised to the treatment, or alternatively allocated to individuals according to how much treatment they actually received. Furthermore the type of non-adherence is potentially important for economic evaluation. A prescription collected from the pharmacy but not taken costs more than a prescription written but never filled. As non-adherence is likely to be correlated with both costs and outcomes of care, the methods used to account for it might also affect the inference drawn from the

cost-effectiveness summary measure. Therefore it is important that trial-based economic evaluations are transparent about the extent of non-adherence and the methods employed to account for it.

The aim of this paper was to review published economic evaluations conducted alongside randomised trials and identify: 1) the proportion reporting information on adherence to the randomised treatments; 2) the methods used for assigning intervention costs to participants according to adherence; 3) which randomised individuals were included in the primary economic analysis; and 4) statistical methods used to estimate intervention cost-effectiveness in those who did adhere to it. We also provide recommendations on improved handling of non-adherence in trial-based economic evaluations.

Methods

Search strategy

The National Health Service Economic Evaluation Database (NHS EED) provides structured abstracts for the majority of economic evaluations in the medical literature [7]. We searched the NHS EED for studies that contained a reference to randomisation or a randomised controlled trial (RCT) by using the search terms “randomi*” and “RCT”. We included economic evaluations with patient-level resource use data collected between randomisation and the primary assessment of outcome in an individually randomised parallel arm RCT of a health care intervention. Exclusion criteria were: non-RCTs, no economic evaluation detailed in the methods, cluster and crossover randomised trials and other designs with within-patient comparisons, trials where the observational unit for adherence was not the participant, feasibility studies, models or long term follow up studies (even if partially based on RCT data) and studies not published in English.

We conducted our search in February 2013 and restricted it to studies published in 2011. This provided a sufficient number of articles reflecting recent methodological practice and NHS EED abstracts were not complete for all studies published more recently.

For economic evaluations which referred to a main trial paper (potentially with more information on treatment adherence), we reviewed both together.

All data was extracted by one author (SLB) using a pre-specified proforma. For studies where there were uncertainties about classification, a second author (WH) also reviewed the article and consensus was reached through discussion.

Experimental treatment arm

For each trial we designated an experimental treatment arm for our analysis. Typically this was the most experimental, newest or highest intensity (e.g. dose) treatment. In situations where this could not be determined (16 trials, 17%), we arbitrarily chose the first treatment arm mentioned within the methods section of the economic evaluation paper.

Non-adherence and treatment intensity

We defined treatment non-adherence as an imperfect correspondence between the intended course of randomly assigned treatment and the actual treatment received [1]. We distinguished between studies of interventions typically intended to be “one-off” in nature (for example, surgery) and those typically intended to be “recurring” (such as behavioural therapy sessions or a course of pharmacotherapy). For all studies, we attempted to ascertain from trial reports the number of participants who received some of their randomly allocated treatment (that is, “initiated”). For "recurring" interventions we also extracted information on the number of participants who adhered to their intended course of treatment (“completed”); and a measure of treatment "intensity" (such as the number of sessions or prescriptions taken). It is common for the intended frequency or duration of treatment to be patient specific (27 trials, 28%), particularly in trials with a recurring intervention where personalised dose titration or stepped care are used. In such studies it may be impossible to calculate how many patients “completed” their intended course of treatment, nonetheless we estimated the proportion of all trials that reported treatment “initiation”, “completion” and “intensity”.

Definition of the analysis set

We recorded the type of analysis used in the primary economic evaluation based on information provided (e.g. CONSORT diagrams) or the author's own definition. Studies analysed participants in the treatment group they were randomised to (“analysed as randomised”) or according to the treatment they actually received (“analysed as treated”). For those that were analysed as randomised, we also recorded whether all randomised participants were included in the analysis (“strict ITT”). Studies often do not include all participants in the analysis – for example, excluding those who withdrew or with no follow up data (“complete case” analysis). Additionally, "per protocol" analyses exclude participants violating the protocol, for example participants not completing treatment or not meeting inclusion criteria.

Methods for costing the interventions

For studies where there was reported non-adherence or a measure of treatment intensity we extracted information about the methods used for calculating intervention costs, provided this was reported in sufficient detail.

We categorised each component of the intervention costs based on three criteria (Table 1): 1) Type of cost (fixed/semi-fixed/variable) [8]; 2) the method for assigning shared costs to participants (indirect/direct); and 3) where applicable, units used for estimating variable costs for individuals. This allowed us to assess the consistency of costing methods used in trials with non-adherence.

We also recorded information on any statistical methods, beyond an as treated or per protocol analysis, to estimate the cost-effectiveness of an intervention in those able to adhere to it.

Results

Our search identified 330 articles; 97 (29%) articles, reporting on 96 unique RCTs, satisfied the eligibility criteria (Figure 1, full list of articles in Supplemental Materials).

For 57 (59%) trials the primary economic evaluation was a cost-effectiveness or cost-utility analysis, whilst in 37 (39%) it was a cost-consequence analysis, 1 (1%) a cost-benefit analysis and 1 (1%) a

cost-minimisation analysis. Interventions evaluated included: 20 (21%) pharmacological; 25 (26%) surgical; 9 (9%) diagnostic; 15 (16%) behavioural/psychosocial/educational (BPE); and 27 (28%) other types of intervention (see Tables S1 and S2 in Supplemental Materials).

Reporting of adherence

37 (39%) trials had a one-off intervention (Table 2), with the majority being surgical. The majority (32, 86%) reported the number of participants initiating treatment, of which more than half (18, 56%) reported having participants who did not initiate the treatment to which they were randomised.

Overall, 59 (61%) trials had a recurring intervention. Of these, 42 had an intervention lasting more than one month, 11 had an intervention lasting less than one month and for 6 there was insufficient information to determine the intervention duration. The majority of trials with a recurring intervention had pharmacological or BPE interventions.

For recurring interventions, the most commonly reported adherence information was the number of participants completing treatment (reported in 73% of trials) and various measures of treatment intensity (reported in 66%). Trials with recurring interventions were less likely to report the number of individuals who initiated treatment, but this information was still reported in over half of papers (56%). Almost all of the trials with a recurring intervention (55, 93%) reported at least one of the measures of adherence (initiation, completion or treatment intensity) but only around one-third (22, 37%) reported all three types. The measure of treatment intensity that was reported appeared to differ slightly across the different types of interventions. Trials with a BPE intervention were more likely to report the number of participants receiving different (discrete) quantities of treatment units. Trials of other interventions often reported the mean, median or total number of treatment units received.

Analysis set used for the primary economic evaluation

For a small number of trials (12, 13%) it was unclear which groups individuals were analysed in (Table 3). In the remaining trials (84, 88%) participants were analysed as randomised; for a number of these trials (n=22), this was inferred from but not explicitly stated in the paper.

In trials where individuals were analysed as randomised, the most common type of analysis was a strict ITT including all randomised individuals (18 trials, 58% of one off interventions and 24, 45% of recurring interventions). An analysis only using complete cases was performed in 18 (34%) trials with a recurring intervention and 5 (16%) trials with a one-off intervention. For both one-off and recurring interventions, around 20% of trials used a per protocol analysis for the primary economic evaluation, for example, excluding participants who were unable to adhere to their treatment. There were a small number of trials where participants were analysed as randomised but the analysis set was unclear.

Intervention costs

Only 13 studies gave a clear description of how intervention costs were calculated and allocated to individual participants (Table 4). The majority of fixed costs were indirectly allocated, meaning the cost of the fixed resource was evenly shared between all participants randomised to the treatment arm regardless of adherence. The exceptions were primarily trials where the cost of the shared resource (for example, equipment, hospital overheads, materials, therapist training, and therapist supervision) was subsumed into the total cost of all resources used in administering the intervention (both fixed and variable) [11,16]. In these cases, the total cost of all intervention resources was used to derive a unit cost for the entire intervention rather than for each resource separately. The unit cost was then directly allocated to participants who received (or adhered to) treatment based on the amount of treatment they received.

Semi-fixed costs were either directly or indirectly allocated depending on the trial. For example, Morris et al. [17] chose to share staff costs for physiotherapists administering a post-surgery rehabilitation programme evenly between all randomised individuals (indirect allocation). Irvine et al. [14] chose to allocate the cost of physiotherapists/facilitators administering lifestyle education sessions only to those who attended (direct allocation).

The measurement units used to directly allocate variable costs depended primarily on the type of resource being considered, but there was some variation across similar resources. For example, staff costs associated with treatment sessions or consultations were generally assigned to individuals based on the number of sessions attended [9,12,21]. The staff (neurosurgeon and anaesthetist) costs

associated with surgery in van den Akker et al. [19] were directly assigned to participants using the number of minutes taken to complete the procedure.

Incorporating adherence into economic evaluations

None of the papers included in our review used statistical methods to adjust for non-adherence or incorporate adherence information directly into the economic evaluation.

Discussion

Main findings

Lack of adherence to randomly assigned treatment and how this is accommodated in the analysis are important issues for the interpretation of economic evaluation conducted alongside RCTs. In more than half of trials there were participants who reportedly did not initiate their randomly assigned treatment. Encouragingly 93% of trials with a recurring intervention and 86% of trials with one off interventions reported at least one measure of adherence. However, treatment adherence is not comprehensively reported – almost 30% of economic evaluations of recurring interventions failed to report the number of participants who completed treatment, and even more (34%) failed to report a measure of treatment intensity. Amongst the 22 (37%) trials with a recurring intervention that did report all three categories of adherence various approaches to reporting were used, with most relying on a combination of flow chart/tables and text (see for example [22-24]).

Approximately 20% of trials reported a primary per protocol analysis potentially excluding participants with low treatment adherence and biasing results. There was little consistency in the assignment of shared costs to individuals, with both direct (reflecting patient treatment adherence) and indirect (ignoring patient treatment adherence) methods being used. None of the economic evaluations incorporated statistical methods to provide an unbiased estimate of cost-effectiveness among treatment compliers.

Strengths and weaknesses

Our study used a systematic approach to identify papers. To our knowledge, it is the first review of adherence reporting and analysis methods in trial-based economic evaluations of pharmacological and non-pharmacological interventions.

Due to journal space constraints, information on the economic methods and results was often sparse, making it difficult to categorise the methods used by authors with certainty. This was particularly the case for trials that report both clinical and economic results in the same article. We did not contact trial authors to verify our interpretation of the methods that they used and we did not review trial protocols. Therefore, we may have misclassified the analysis set or cost allocation methods used. Furthermore, we restricted our analysis to the most recent year of economic evaluations with complete data available in the NHS EED. Our review, however, provides a snapshot of treatment non-adherence reporting and analytical methods as described in recent trial-based economic evaluations.

The relationship between intervention costs and treatment adherence is often complex. For example, in van der Meer et al. [10] an electronic spirometer was provided to each patient for home monitoring of asthma. Once the spirometer has been given, the cost is incurred regardless of subsequent adherence. If a patient was to withdraw from the trial immediately after randomisation, however, and then it is possible that the cost of the spirometer could be avoided. Due to such complexities, it is very difficult to judge from an economic evaluation report whether costing methods have appropriately accounted for these opportunity costs of treatment adherence [25].

Comparison with previous research

The issues considered here bridge two relatively disparate areas of previous research. First reviews considering the reporting and appropriate analysis of non-adherence in clinical trials [1,4,26]. Second research on the impact of drug non-adherence on the costs and outcomes of care, which has been primarily evaluated using decision analysis models [2,27-29]. Most of these authors have highlighted the need for improvements in the collection of adherence data and clear definitions of the types of non-adherence being measured. Our review suggests such improvements are also needed for the reporting of trial-based economic evaluations.

Dodd et al. [1] found the number of patients initiating treatment was reported in 50%, 68% and 83% of trials with long-term, short-term and one-off interventions, respectively. They also found that 77% of trials with short- or long-term interventions at least partially reported the number of patients completing treatment. These figures compare closely with our findings (Table 2). Zhang et al. [4] found slightly less than half (46%) of trials with an oral pharmacological intervention reported adherence results whilst Gossec et al. [26] found even lower rates. We found higher adherence reporting rates, 63-79% depending on the aspect of treatment adherence being considered. This may be because economic evaluations are more likely to provide details of treatment intensity in estimating the cost of health care.

Hughes et al. [29] found that adherence was not included routinely in pharmacoeconomic analysis based on decision analysis models and recommended that net-benefit regression, including a treatment and adherence interaction term, would allow trial-based economic evaluations to explore any impact of non-adherence on cost-effectiveness. Despite this recommendation, none of the economic evaluations included in our review used this approach to explore the impact of adherence.

Implications

We found that the reporting of adherence in trial-based economic evaluations was not comprehensive. Numerous definitions of non-adherence appear in the economic literature and this increases the challenges with making comparisons across studies [2]. Appropriate definitions of adherence may also depend on the context of the study and the type of intervention. Some authors have provided useful guidance on the measures of adherence that trials should report [1]. This guidance applies equally well to the reporting of economic evaluations. For medication use in particular, formal definitions of compliance and persistence have already been proposed [30]. Failure to provide adequate information on adherence makes it difficult to synthesize results of trials with different degrees of adherence or to generalise trial results to clinical practice where adherence to therapy may be different.

We found that only a small number of papers reported costing methods in sufficient detail for us to determine exactly how intervention costs were allocated at an individual patient level. There was

variable practice in how studies directly or indirectly assigned shared costs to participants based on their degree of adherence. For variable resources, we found that some trials chose to directly allocate costs based on much greater levels of detail (for example, per minute for the use of the operating room or specialist staff time in van den Akker et al. [19]) whereas others used less detail and applied an average unit cost based on a higher level of aggregation (for example, per consultation for nurse consultations in Chuang et al. [9]). The widely cited textbook on economic evaluation by Drummond et al. states that "…there is no unambiguously right way to apportion [shared] costs" and that "...analysts need to form a judgement on how accurate (or precise) cost estimates need to be within a given study" [31]. Direct allocation of costs according to the precise amount used by each patient is likely to produce the most accurate individual cost estimates and allow the most detailed exploration of the relationship between adherence, costs and outcomes. Simple methods for assigning costs (for example, indirect assignment of fixed costs to participants regardless of adherence to treatment) have the potential to under-estimate the variance in costs between individuals and therefore the confidence interval surrounding the net monetary benefit statistic.

Poor reporting also made it difficult to judge the analysis set used to estimate cost-effectiveness. For many papers the analysis set used in the economic evaluation had to be inferred from the results presented. The CONSORT statement recommends that papers clearly describe the specific set of participants included in each analysis [5]. Likewise the recent CHEERS checklist for reporting economic evaluations highlights the importance of stating whether ITT analysis was used and methods for handling missing data [32].

In those studies that provided sufficient information, the most frequent primary analysis set was ITT using a complete or partially imputed dataset. This seems appropriate given that economic analyses are most likely to be conducted alongside phase III pragmatic trials aimed at informing policy. The key benefits of ITT analysis are that it decreases potential for selection bias by preserving randomisation as well as providing a "real world" estimate of cost-effectiveness, attenuated by non-adherence. Interestingly, the impact of non-adherence on cost-effectiveness results from an ITT analysis will depend on whether the incremental cost effectiveness ratio (ICER) or net monetary benefit (NMB) is used to summarise results (see appendix in Supplemental Materials). Under plausible assumptions, the ITT ICER remains constant as the adherence rate varies. On the other hand the NMB is affected

by the rate of adherence and approaches zero as non-adherence approaches 1. Therefore in trial-based economic evaluation aimed at informing policy the NMB is likely to be a more appropriate cost-effectiveness summary measure. Such results can be shown explicitly for a trial in which participants are exclusively adherers or non-adherers (for example, a surgical trial), however in a trial where partial adherence is possible (for example, pharmacological trials) the resulting impact of non-adherence on the ITT ICER and ITT NMB may be further complicated. It is also worth noting that adherence in a trial may be better than in routine practice, for example, due to increased patient monitoring or the selection of trial participants based on their ability to adhere to treatment. The impact of this on cost-effectiveness is ambiguous [6].

We found that only around half of studies actually used a strict ITT analysis. In some studies it may be impossible to include all patients for reasons of missing data or protocol violations. The FDA guidance on 'Statistical Principles for Clinical Trials' refers to a 'full analysis set' which they define as "the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomised subjects" [33]. It is likely that a number of studies in our review which did not use a strict ITT analysis were still attempting to follow the ethos of such guidelines.

Although ITT analysis is optimal for assessing the pragmatic question of whether a policy of assigning patients to a given therapy is likely to be cost-effective despite imperfect adherence to therapy, ITT analyses do not shed light on the relationship between adherence and cost-effectiveness. Understanding this relationship is crucial for distinguishing an intervention that is not cost-effective even in participants who adhere to it from one that is not cost-effective because a high proportion of individuals do not adhere to it. For the latter, there may be a case for 'compliance-enhancing' modifications to treatment to improve cost-effectiveness [34,35]. Furthermore, details on cost-effectiveness among adherers may be valuable for assessing the transferability of trial results, through decision analysis models, to other settings where adherence is known to differ.

A small proportion of studies used a per protocol comparison as the primary analysis to examine cost-effectiveness in those that adhered to treatment. This potentially introduces selection bias as the comparison is no longer between randomly allocated treatment groups (see appendix in Supplemental Materials). Several methods exist for estimating the causal treatment effect in trials with non-adherence [36]. Instrumental variable analysis [37,38] is likely to offer the simplest starting point

and this approach could be readily extended to net monetary benefit analysis. A lack of examples in the cost-effectiveness studies we identified suggests this is a fertile area for further applied and methodological research.

Recommendations

1) A CONSORT diagram should be included with all trial-based economic evaluations detailing exactly which trial participants are included in the analysis set used for the primary and secondary economic analysis.
2) Key items of adherence to be measured during the trial should be pre-specified. More detailed recommendations on the appropriate measures of adherence have been described elsewhere [1,30]. There should be, however, transparent reporting of these key items of adherence within the report of the trial-based economic evaluation.
3) Greater justification and detail should be provided (in the main report or in an appendix) on the methods used to allocate shared costs to individual participants who adhere or do not adhere to treatment.
4) If non-adherence is prevalent, then trial-based economic evaluations aimed at informing policy should report primary ITT analyses based on the NMB rather than the ICER. Under plausible assumptions it can be shown that the ICER is invariant to the rate of non-adherence, whereas the NMB is influenced by changes in the adherence rate (see appendix).
5) As a sensitivity analysis statistical methods to estimate cost-effectiveness in participants who adhere to treatment should be considered. A per protocol analysis will not provide an unbiased estimate. The ITT ICER will provide such an estimate under certain assumptions (see appendix). Alternatively, an instrumental variable approach applied to the NMB may be appropriate.

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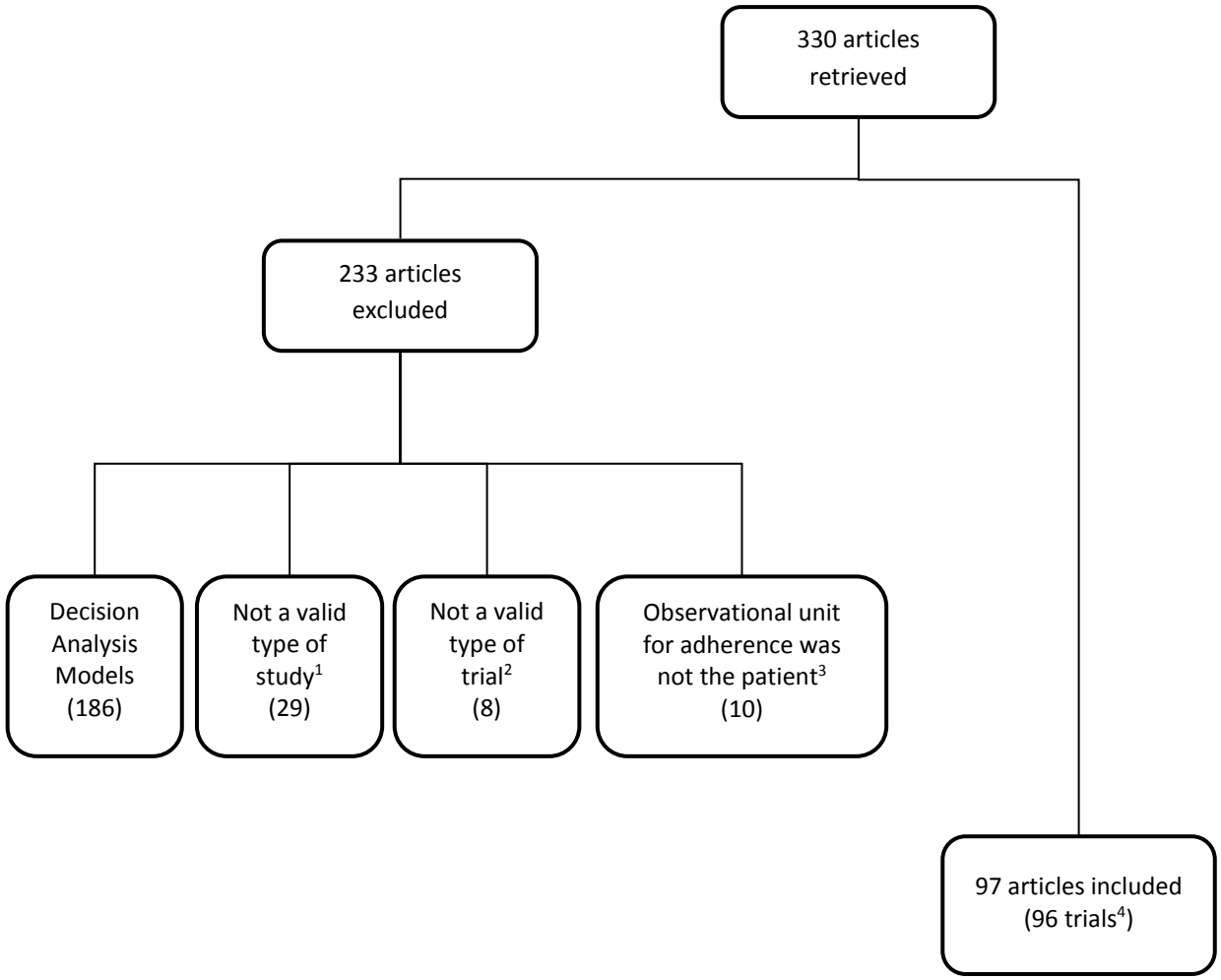
Figure 1. Study flow chart



Notes. [1] Includes five review papers, one symposium paper, two feasibility studies, two studies not reporting within-trial results, two studies which did not discuss costs in the methods section and 17 studies where participants were not randomised. [2] Includes eight cluster randomised trials. [3] For example, where ventilation systems were installed into homes. [4] There were three Health Technology Assessment reports which related to trials published in a separate article already in our review. Additionally, there were two articles which each reported two trials.

Table 1. Criteria used for assessing methods used to calculate patient-level intervention costs.

	Categories	Definition	Example
1. Type of intervention cost			
	Fixed costs	Shared costs which are not affected by within-trial adherence to treatment.	Costs of developing software for internet based management for patients with asthma.
	Semi-fixed costs	Shared costs which are fixed for a given range of adherence to treatment, but change in steps above a given threshold.	Staff costs for a physiotherapist leading group lifestyle intervention sessions for which one session would be required if 1 to 12 patients adhere, two sessions would be required if 13 to 24 patients adhere, and so on.
	Variable costs	Costs which vary proportionately with changes in activity at the individual patient level.	Costs associated with drugs and consumables.
2. The method used for assigning shared costs to patients			
	Indirect allocation	Costs are allocated to all patients for whom the resource was intended regardless of the amount of resource an individual patient used.	The cost of developing the software is shared between all patients who were randomised to the intervention arm intended to receive internet based management of their asthma.
	Direct allocation	Costs are allocated to patients in direct proportion to the amount of the resource that they used.	Only patients who attend their group lifestyle session are allocated the staff costs of the physiotherapist who is leading it.
3. Units used for estimating variable costs for individual patients			
	n/a	The measurement units used to estimate variable costs.	Cost per consultation or cost per minute might be used for a GP visit

Table 2. Number of trials reporting adherence and measures of treatment intensity for the experimental treatment arm

	One-off interventions				Recurring interventions			
	Surgical (n = 25)	Diagnostic (n = 7)	Other[1] (n = 5)	Total (n = 37)	Pharmacological (n = 19)	BPE (n = 15)	Other[1] (n = 25)	Total (n = 59)
Reported the number of participants initiating treatment	22 (88%)	6 (86%)	4 (80%)	32 (86%)	13 (68%)	7 (47%)	13 (52%)	33 (56%)
≤95%	6 (27%)	3 (50%)	1 (25%)	10 (31%)	3 (23%)	4 (57%)	7 (54%)	14 (42%)
>95%, <100%	6 (27%)	1 (17%)	1 (25%)	8 (25%)	3 (23%)	1 (14%)	3 (23%)	7 (21%)
100%	10 (45%)	2 (33%)	2 (50%)	14 (44%)	7 (54%)	2 (29%)	1 (8%)	10 (30%)
Not reported for each treatment arm[2]					0 (0%)	0 (0%)	2 (15%)	2 (6%)
Reported the number of participants completing treatment	-	-	-	-	15 (79%)	12 (80%)	16 (64%)	43 (73%)
Reported measure(s) of treatment intensity[3]					12 (63%)	11 (73%)	16 (64%)	39 (66%)
Number of participants receiving different (discrete) quantities of treatment	-	-	-	-	1 (8%)	7 (64%)	1 (6%)	9 (23%)
Mean/median/total number of treatment units or treatment exposure (e.g. time) received by participants	-	-	-	-	7 (58%)	6 (55%)	12 (75%)	25 (64%)
Percentage of treatment units successfully administered to participants	-	-	-	-	0 (0%)	0 (0%)	1 (6%)	1 (3%)
Percentage of participants achieving a treatment threshold	-	-	-	-	4 (33%)	2 (18%)	3 (19%)	9 (23%)

Notes. [1] Details of the other types of interventions are given in the appendix. [2] One trial reported the number of participants initiating treatment by factor level (but not by treatment arm) and one trial reported the number of participants initiating treatment overall. [3] Trials may have reported more than one measure of treatment intensity. BPE: Behavioural/Psychosocial/Educational.

Table 3. Analysis set used for the primary economic evaluation

	One-off interventions (n = 37)	Recurring interventions (n = 59)
Analysed as randomised[1]	31 (84%)	53 (90%)
Strict ITT (complete data or use of imputation[2])	18 (58%)	24 (45%)
Complete case	5 (16%)	18 (34%)
Per protocol[3]	3 (10%)	7 (13%)
Per protocol[3] & complete cases	3 (10%)	3 (6%)
Analysis set unclear	2 (6%)	1 (2%)
Analysed as treated	0 (0%)	0 (0%)
Unclear	6 (16%)	6 (10%)

Notes. [1] 11 trials with a one-off intervention and 11 trials with a recurring intervention did not explicitly state that they analysed participants as randomised but this was able to be inferred from the results tables. [2] There were a total of 27 trials overall which reported using imputation for missing economic outcomes (costs, effects or both): 15 (4 one-off and 11 recurring) of these performed a strict ITT whilst 12 (1 one-off and 11 recurring) performed a per protocol and/or complete case analysis (i.e. only imputed missing outcomes for a selection of patients). [3] Reasons for being classified as a per protocol analysis include: the authors stating a per protocol analysis; excluding participants who didn't satisfy the inclusion criteria (after randomisation); excluding participants who didn't initiate treatment; excluding participants for treatment complications, treatments switching or converted surgical procedures. ITT: Intention-to-treat analysis.

Table 4. Categories of intervention costs and the methods for assigning costs to study participants.

Paper	Analysis set for primary economic evaluation	Intervention	Cost component	Fixed, semi-fixed or variable cost	Direct or indirect allocation	Units used for direct allocation
Chuang et al. [9]	Strict ITT	Ultrasound therapy for patients with hard to heal leg ulcers				
			1 Ultrasound machines	Fixed	Indirect	NA
			2 Nurse consultations	Variable	Direct	Per consultation (by treatment location)
			3 Compression therapy	Variable	Direct	Per consultation (by high/low compression applied)
van der Meer et al. [10]	Strict ITT	Internet-based self management for patients with asthma				
			1 Materials (software support, electronic spirometer)	Fixed	Indirect	NA
			2 Personnel time (development educational aids, group education sessions, data review and patient communication)	Semi-fixed	Indirect	NA

		3	Patient costs (travel, time, Internet and text messaging costs)	Variable	Direct	Per treatment session, login or text message
Wordsworth et al. [11]	Strict ITT	Clomifene citrate treatment for couples with unexplained infertility				
		1	Equipment (scanning machines and couches)	Fixed	Direct	
		2	Hospital overheads (administration, heating, cleaning, property maintenance)	Fixed	Direct	Per treatment cycle[1]
		3	Staff time (nurse, subfertility sister, receptionist, secretary, senior registrar)	Fixed	Direct	
		4	Consumables	Variable	Direct	
Hopkins et al. [12]	Strict ITT	Nephrologist/nurse-based multifaceted intervention for patients with stage 3 to 4 chronic kidney disease				
		1	Nephrologists' time (visits, meetings, communications)	Fixed	Indirect	NA
		2	Nurse visits	Variable	Direct	Per visit
Hedman et al. [13]	Strict ITT	Internet-based cognitive behaviour therapy for patients with social anxiety disorder				

		1	Therapist time (spent responding to patient messages)	Variable	Direct	Per minute
		2	Patient time (domestic loss)	Variable	Direct	Per minute
Irvine et al. [14]	Strict ITT	Lifestyle intervention (including group education sessions, peer support sessions, physiotherapy and telephone peer support) for patients at higher risk of developing diabetes				
		1	Telephone peer support staff (volunteers) training costs	Fixed	Indirect	NA
		2	Facilitator and/or physiotherapist time for administering various group sessions	Semi-fixed	Direct	Per treatment session (unit cost dependent on attendance rate)
		3	Telephone peer support staff (volunteers) time	Variable	Direct	Per minute
Mittman et al. [15]	Per protocol	Budesonide/Formoterol added to tiotropium for treating patients with chronic obstructive pulmonary disease				
		1	Study drugs	Fixed	Indirect	NA
Patel et al. [16]	Complete cases	Motivational enhancement therapy (MET) and cognitive behaviour therapy (CBT) for patients with Type 1 diabetes				
		1	Materials (manual, information sheets, Accu-Test CD-ROM, tape recorder, tapes)	Fixed	Direct	Per treatment session (by session type: MET/CBT)[2]
		2	Therapist training	Fixed	Direct	
		3	Therapist supervision	Fixed	Direct	

		4	Therapist time for delivery of treatment sessions	Variable	Direct	
		5	Therapist time for chasing non-attenders	Variable	Direct	
Morris et al. [17]	Unclear	Rehabilitation programme (12 supervised group exercise classes) and an educational booklet for patients who have undergone discectomy or lateral nerve root decompression surgery				
		1	Booklet cost	Fixed	Indirect	NA
		2	Staff costs (physiotherapist) for the rehabilitation programme classes	Semi-fixed	Indirect	NA
Whitehurst et al. [18]	Strict ITT	Acupuncture (as an adjunct to exercise-based physical therapy) for patients with osteoarthritis of the knee				
		1	Study treatment sessions (advice and exercise with/without acupuncture)	Variable	Direct	Per treatment session (by session type)
van den Akker et al. [19]	Strict ITT	Tubular diskectomy for patients with lumbar disk-related sciatica				
		1	Operating room (including standard staff, equipment and overheads)	Variable	Direct	Per minute
		2	Specialist staff (neurosurgeon and anaesthetist)	Variable	Direct	Per minute
		3	Specific operating equipment (incorporating	Fixed	Indirect	NA

			purchase price, yearly use, depreciation, maintenance and interest)			
		4	Consumables	Variable	Direct	Per item
Thomas et al. [20]	Complete cases	Ion-exchange water softener installed into the home of children with atopic ezcema				
		1	Ion-exchange water softener	Fixed	Indirect	NA
		2	Installation	Fixed	Indirect	NA
		3	Salt	Variable	Direct	Per salt box[3]
		4	Consultation	Variable	Direct	Per consultation
Cockaykne et al. [21]	Complete cases	Cryotherapy using liquid nitrogen for patients with verrucae (plantar warts)				
		1	Equipment	Fixed	Direct	Per treatment session[4]
		2	Liquid nitrogen	Variable	Direct	Per treatment session
		3	Clinician's (GP, nurse or podiatrist) time	Variable	Direct	Per treatment session

Notes. [1] Unit cost for each treatment cycle was hospital specific (n=5) and based on the total cost of all resources used for the intervention, divided by the total number of treatment cycles delivered by that hospital. [2] Unit cost for each type of treatment session (MET/CBT) was based on the total cost of all resources used in delivering that session type. An average cost per session/per person was derived based on "assuming 20% higher attendance rates". [3] Allocated based on assumed (rather than actual) consumption, determined using number of residents in the house. [4] Unit cost based on the total annual cost of the equipment divided by the maximum number of treatments it could provide in a year (assuming an average of 20 minutes per treatment session). NA: Not applicable. ITT: intention-to-treat.