Title: Making sense of economic evidence in understanding the value of interventions for severe asthma.

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1. Introduction

Severe asthma has been identified as an area of high, but potentially avoidable, morbidity and cost in relation to the overall burden of asthma[1]. Given increased understanding of the role played by patient-related factors (e.g. psychological or socio-economic problems) in contributing to severe asthma, psycho-educational interventions, combined with known pharmaceutical therapies, are increasingly being advocated and implemented for its management (see Appendix 1 for an overview of the current state of knowledge in this field). These interventions include a complex mix of active education, training in self-management and/or the targeting of specific psychosocial issues resulting from, or impacting on, asthma. To investigate the effectiveness and cost-effectiveness of such interventions we conducted a systematic review of a range of psycho-educational interventions for patients with severe asthma (see Appendix 2 for more detail) and an economic evaluation alongside a randomised controlled trial (RCT) of a specific psycho-educational programme for poorly compliant adults with severe asthma (see Appendix 3 for more detail).

Although there is increasing emphasis on the importance of quality and consistent methodology in designing and evaluating such complex interventions[2], and growing interest in the systematic review field regarding appropriate ways to summarise and report relevant features of these types of interventions[3], the conduct and reporting of *economic* studies alongside these is not yet subject to specific recommendations. Further, there is a lack of guidance on when, and how, the reporting of economic evaluations of individual interventions should be linked to systematic reviews[4].

This paper therefore presents our progress to date with deriving and reporting appropriate conclusions from our two (one primary, one secondary) research studies concerning the cost-

effectiveness of complex psycho-educational interventions for severe asthma. In particular, we explore issues related to: (1) assessing and interpreting costs; (2) measuring and valuing benefits; and (3) reporting results from the economic evaluation in light of the findings from the RCT and systematic review. After summarising existing thinking around the economics of asthma care, the paper is structured around these three key areas. Although the paper is, naturally, set within the context of complex psycho-educational interventions for severe asthma, we believe many of the issues apply across multi-faceted interventions for a range of patient groups with chronic diseases or multiple problems that are affected by lifestyle and other patient characteristics. We therefore welcome advice, comment and discussion from those who have experience of evaluating and reporting on such interventions beyond the asthma field.

2. Issues in the economic evaluation of asthma care

Discussion papers on the economics of asthma indicate a growing awareness that socio-economic conditions for patients, and resource constraints in the health service, affect the need for, and success of, programmes directed at improving asthma management[1,5,6]. Reviews focussing more specifically on economic studies of asthma *treatments* indicate that the majority are cost minimisation analyses of management strategies in *routine* asthma care, with emphasis on effective delivery and uptake of *pharmacological* treatments[7-12]. Although several reviews of economic studies of specific psycho-educational interventions[13-16] highlight individual studies that suggest asthma self-management education programmes are more cost-effective than routine care in *general* adult populations[17,18], few have taken a systematic or critical approach to reviewing the literature. When this has been done, in common with many concurrent reviews of economic studies in general, the quantity and quality of economic analyses in this field have been found wanting[10]. A number of authors also emphasise the difficulty of generalisation from the current research evidence, particularly to patients with *severe* asthma and, given that the majority of existing studies have been conducted in the US, the UK health service setting[1,10,12]. It is thus still uncertain whether higher resource use and costs in patients with severe asthma could be reduced by better management of the illness, such as might be achieved through psycho-educational interventions.

With respect to economic analyses in the asthma field, difficulties include defining, measuring and valuing outcomes that are generalisable across the spectrum of asthma patients (and interventions) [9,19], the lack of good observational data to support accurate and comprehensive assessment of costs[9,12] and a lack of guidance for the presentation of new economic evidence in the context of existing research[4]. Issues related to the appropriate identification, assessment and valuation of costs and benefits, and the suitable presentation of findings, are further complicated when examining

complex interventions (e.g. psycho-educational programmes) in complex patient groups (e.g. patients with severe asthma) as opposed to more 'traditional' evaluations of, for example, drug treatments for acute disease. Our experience in handling these issues is reported below.

3. Assessing and interpreting costs

This section uses examples from our own research to illustrate two key issues relevant to the appropriate assessment and interpretation of cost data when evaluating complex interventions.

3.1. Comprehensive assessment of costs

The importance of considering costs *comprehensively* is emphasised in previous reviews of economic evaluations in asthma[7-9]. Since resource use and the costs of implementing interventions are likely to be high amongst complex chronic disease groups, and the targets for intervention long-term problems, this issue is particularly pertinent in this context. However, our systematic review suggests that even on the rare occasions that studies do formally consider costs, this is not done comprehensively. But what does *comprehensively* mean here?

Our systematic review considered 22 adult studies suitable for in-depth review, on the basis of appropriate targeting to patients and study design (see Appendix 2). Of these only four (including our own RCT) ultimately reported any assessment of costs in monetary terms. Two reported limited inpatient costs, and another "direct health care costs" (where it was not clear what these covered). Only our own RCT undertook detailed costing of all health and social service resource use (as outlined in Appendix 3) and separately reported the cost of the psycho-educational programme (see Table 7, Appendix 3), so it was not clear in other studies whether interventions been fully costed. Three of the four studies reported differences in costs of health care, including the intervention cost (see Table 5, Appendix 2). Two showed a net saving (although this was not formally quantified in the report for one study) and our own study reported a net increase in costs (see Table 7, Appendix 3). The remaining study did not report sufficient data to estimate cost differences between groups. The differences between groups in the studies showing net savings resulted from small reductions in health care use combined with high unit costs of utilization since these studies were conducted in the US. Only our own RCT fully estimated productivity costs and patient costs (note, though, that full costings of lost work and other patient time, travel and out-of-pocket expenses are yet to be done, although preliminary analyses suggest that there are likely to be no significant differences between groups, and thus these will not alter the conclusion).

This raises two issues in relation to the *comprehensive* assessment of costs. First, what does comprehensive mean in terms of the *breadth* of coverage of costs? Should studies consider the potential impact of these complex interventions on resource use and other costs unrelated to the primary disease/problem under study? In our study we considered a wide range of costs, related to asthma *per se*, but also other health, psychological or social problems. Other studies did not. We also considered wider non-health sector costs (principally social services), patient costs and productivity costs. Again, other studies did not. Our rationale for this was that the implementation and effects of complex psycho-educational interventions often encompass more than 'just' health, such as liaison and referral to social and other services. Psycho-educational interventions in children with asthma often also encompass the education sector and other social interventions may go wider still. But this begs the question of how wide should one go in assessing costs, and who should ultimately bear these costs i.e. what is the appropriate perspective taken in terms of deciding on funding for these types of interventions? Similarly, the impacts on productivity costs in patients with severe disease, or multiple problems, are mainly likely to be mediated via effects on the uptake of, and need for, welfare benefits. This implies a need for better tools for valuation of effects on 'hidden' household economies (rather than just the formal 'productive' sector) in economic analyses in these groups. Since these are lacking, and in our study at least inclusion of indirect costs appears unlikely to influence conclusions, is it practical and appropriate to assess these costs?

Second, what does comprehensive mean in terms of the *depth* of costing? In our RCT we undertook a detailed analysis of resource use to the various parties involved. Such effort in pursuing a 'micro-costing' is considerable, in terms of data collection, entry and analysis. However, many of the 'micro costs' appeared to have little influence on the overall conclusion generated by using key health care costs (e.g. admissions). Further, the results of our RCT (Table 6, Appendix 3) demonstrate that the intervention had little impact in terms of effectiveness, thus making any information on cost redundant in the recommendations. Is it therefore worth expending research effort on this element of the evaluation prior to, or concurrently with, estimations of effectiveness? Would it make more sense to determine effectiveness, together with broad indications of cost from major elements (such as admissions), and then pursue micro-costing as a second stage if effectiveness differs and/or the broad cost calculation indicates a possible difference? If so, how would this be done and would the fact that patient-reported data may not be available at a later stage alter conclusions? Furthermore, with respect to this issue, what is the added value of undertaking specific local unit costings, rather than using unit costs based on available generic cost data (e.g as provided by PSSRU)? Again, undertaking the former has resource implications for conducting the research, so what is the likely 'added value'?

3.2. Compliance issues

Compliance, with appointments, medications and other self-care activities, is generally seen to be a 'good thing'. In our RCT, for example, poorly compliant patients were specifically targeted, as this group were deemed most likely to be at risk from adverse outcomes. However, it is not clear how the resource implications of poor compliance or improved compliance should be handled. Our results suggest that the intervention had no major impact on self-reported compliance with medication or patterns of attendance. However, our results demonstrate a (non-significant) higher level of health care costs amongst intervention patients than control patients, even disregarding the cost of the intervention itself. We are yet to fully explore the reasons for this and it may reflect the influence of a small number of "high users" in the intervention group. Yet, would it be surprising, given that they aim to improve compliance, if interventions of this kind led to increased costs, particularly if the costs of poor compliance (e.g. failed attendances at appointments) are not considered? Increased awareness of, for example, the disease, symptoms, possible treatments or preventive measures, might result in increased fulfilment of prescriptions and earlier or more frequent attendance, thus increased costs. This might also occur in the absence of any (short-term) improvements in health outcomes given the complex relationship between compliance and chronic disease and the fact that optimal levels of medication use and attendance in asthma, particularly among severe groups, are yet to be established. The core economic rationale for implementing psycho-educational interventions in asthma is that it will reduce use of emergency and inpatient use, and reductions in these will off-set the cost of implementing the intervention. However, our trial and other studies from our systematic review suggest this is not necessarily the case. Should the costs of poor compliance be taken into account? Do these issues require more careful consideration?

4. Measuring and valuing benefits

There are a number of issues related to measuring and valuing the benefits of interventions for economic analyses in the asthma field that are magnified when considering complex interventions in patients with severe disease or multiple problems.

4.1. Problems with existing measures

The growing empirical literature on outcomes measurement in asthma includes consideration of problems related to the development of outcomes suitable for inclusion in economic analyses[20-23]. There are increasing recommendations towards combining both generic and asthma-specific quality of life instruments[20] and/or composite symptom measures[19,24,25]. Despite this, the most commonly

reported ‘outcomes’ found in our systematic review, including the four studies undertaking economic analyses, were hospital admissions and emergency attendances (see Appendix 2). Clearly this can lead to double-counting since these ‘outcomes’ should be considered on the cost side of the equation. Studies using these measures infer economic gain by comparing any cost-savings resulting from changes in admissions or emergency attendances with the cost of the intervention, with no reference to (the value of) change in health status. So, what should we do?

Composite measures of asthma symptoms (e.g. episode-free or symptom-free days[19]) have been criticised because of: (1) circularity in the definitions they use (e.g. feeling better may result in doing more (e.g. exercise) which results in more ‘symptoms’ but would indicate overall improved health)[21]; (2) potential lack of sensitivity in either mild (where symptoms are rarely experienced) or severe (where symptoms are experienced everyday) disease; and (3) patients not necessarily assigning equal weights to different symptoms, particularly at different levels of severity[24]. Attempts to overcome the latter have been made, but preference-based measures of asthma symptoms have not yet been widely used or validated for use amongst severe disease groups[24,25]. In addition, in patients with severe or multiple problems, disease-specific measures fail to capture the likely effects of complex interventions on other physical and psychological co-morbidities. For this reason, in our RCT the primary outcome for the economic analysis was a generic measure of health status (SF-36) used alongside an asthma specific quality of life scale and a measure of symptom control (see Appendix 3) for the clinical evaluation. The SF36 was chosen in preference to other generic quality of life scales since it also allows derivation of utilities to facilitate the conduct of a cost-utility analyses, and has shown to be relatively sensitive in asthma compared to other generic utility instruments (e.g. EQ-5D)[8,21]. All our primary outcomes showed consistent findings at the 6 month primary study endpoint; namely, no differences between groups (see Table 6, Appendix 3). However, we could have had a problem of interpreting conflicting data from combinations of generic and disease-specific measures, as has been noted by others[26]. What, therefore, should the recommendations for future similar studies be?

4.2. Comprehensive assessment of benefits

As for costs, the importance of considering outcomes comprehensively is emphasised by existing commentaries on economic studies in asthma[7-9]. The focus of evaluations of many complex interventions, however, remains on ‘health outcomes’ (i.e. patient health status) and few studies assessed in our systematic review considered the potential broader impacts of psycho-educational programmes. Although the primary outcomes in our trial were health-related we recognised the potential for other impacts, for example, on patient psychology and behaviour. We observed short-

term (2 month) changes in self management behaviour (use of reliever inhaler and monitoring of peak flows) in the intervention group, but these changes were not sustained and did not appear to have any knock on effect on health outcomes at any follow up point (see Appendix 3).

Despite this, all intervention patients interviewed at 6 months follow-up (see Appendix 3) identified benefits. Twenty-three control patients identified *potential* personal benefits from the programme as described to them, and an additional 16, benefits for other people which largely reflected those identified by others as personal benefits and are thus not reported here. The numbers of people in each group identifying the different types of personal benefit, and where they were identified the mean weighting given to each benefit (out of 100 points to allocate amongst the benefits identified by each patient), along with rankings based on each of these, are shown in Table 1.

Table 1 Perceptions of benefits and relative weightings from intervention and control patients

Benefit	**Intervention (N=41)**				**Control (N=23)**			
	No. identifying	**Rank**	**Mean weight**	**Rank**	**No. identifying**	**Rank**	**Mean weight**	**Rank**
Education	21	1	40.86	5	11	1	49.27	1
Better management	18	2	39.67	6	1	=9	30.00	11
Time	12	3	37.83	9	1	=9	33.00	=8
Relationship	10	4	38.90	7	6	=4	38.17	5
Practical help	7	=5	38.57	8	3		33.33	7
Reassurance	7	=5	46.14	3	7	=2	46.14	4
Motivation	5	=7	35.20	10	2	=7	33.00	=8
Asthma/health outcomes	5	=7	41.60	4	2	=7	46.50	3
Convenience	4	9	60.75	1	5	6	31.80	10
Phone access	3	=10	29.33	11	7	=2	38.00	6
Social Contact	3	=10	50.00	2	6	=4	47.67	2
Other	2	-	40.00	-	2	-	33.00	-
Unspecified	1	-	-	-	1	-	-	-

There are clear differences between actual and anticipated benefits (intervention and control patients). It is worth noting, however, that improvements in asthma and health outcomes, the primary outcomes of the study, are well down the list in terms of actual or anticipated benefits from the programme. Most commonly cited and highly weighted by both groups are anticipated educational outcomes in terms of increased knowledge etc, but it is well known that improvements in knowledge do not correlate well with changes in behaviour. Amongst the intervention patients, however, factors related to better management of asthma were the second most commonly cited benefits perceived. Self care behaviour (e.g. compliance, peak flow monitoring, trigger avoidance, attack management, coping) was assessed in our study but as highlighted the only changes observed were short-term, not sustained and not reflected in changes in health outcomes. That prolonged

changes in self care behaviour or psychological variables associated with it (e.g. confidence) were not noted could, however, be reflective of the lack of good measures to assess these factors, which is a focus of the main author's PhD.

Many of the benefits experienced or anticipated from the programme are 'intangible' and unlikely to be picked up by traditional methods of benefit measurement. How important are they? Should we be concerned about them in these types of interventions given a lack of data on their ability to influence health outcomes or quality of life? Is further exploration of benefits needed if the primary health outcomes of a trial are not shown to be different? The latter will probably depend on the perspective taken for the evaluation and links back to some of the issues related to costs.

4.3. Valuing wider benefits

In considering the importance of these wider 'intangible' benefits, one possible method that may capture broader impacts of complex interventions is to use contingent valuation techniques. These have begun to be seen in the asthma field[23], including in determining the hypothetical value of self management programmes (where respondents were mailed information and contacted for telephone interview, giving a 30% response rate and mean patient willingness to pay of $29.50 for an 8 week programme)[27]. Although these studies demonstrate the possible feasibility of obtaining willingness to pay (WTP) for asthma management programmes, they were little help in our RCT as in these studies not only did patients not actually get the intervention, but those expressing WTP had scores on questionnaires indicating that they were motivated to self manage their asthma, had good access to health care resources and had skills to manage their asthma (although it was noted that their asthma education could be improved). Our circumstance was somewhat different. Principally, we were dealing with a group who were not necessarily motivated to manage their asthma (some, for instance, even preferred not to have their asthma improved for fear of having sickness benefit removed!), did not necessarily have the skills or resource to self-manage effectively, and most had very low levels of income (see Appendix 3). We therefore tried a method of obtaining patient willingness to accept (WTA) compensation, framed as a payment from the NHS to enable them to 'buy' the intervention or substitute it with other measures they felt would offer them more benefit (see Appendix 3). Within each group, two forms of question were applied - one using a payment scale of £0 to £100, and another of £0 to £1,000,000. All but one patient available for follow up at 6 months agreed to answer the question on WTA payment. The results are presented below.

Table 2 Descriptive data on levels of payment patients were willing to accept instead of receiving the programme

	Intervention group	**Control group**

	£100 card (N = 13)	£1m card (N = 27)	£100 card (N = 13)	£1m card (N = 26)
Mean (SD)	468 (1362)	327,911 (454582)	1600 (5529)	196,917 (399,764)
Median (IQR)	100 (0)	20,000 (997,000)	100 (105)	2000 (27,495)
Mode	100	1,000,000	100	5
Range	30 - 5000	10 – 1,000,000	5 - 20,000	0 – 1,000,000

Four control patients and 11 intervention patients given the £100 scale chose the maximum or more, and five control and eight intervention patients given the £1m scale chose the maximum. These respondents commented that "no amount of money would be enough", "money wouldn't help/makes no difference", "health cannot be valued", "health is more important than any amount of money" etc. However, several also commented that they wouldn't spend any money given in compensation on asthma anyway! Of those selecting WTA amounts below the maximum, rationales given for their choice included "equivalent to prescription costs for a year" and "equivalent to a private consultant fee". Those who choose minimal or no compensation were generally those in the control group who did not identify any potential personal benefits from the programme and stated that they actively would not want it or felt that it should be provided to people more needy than themselves. Apart from the highly significant difference caused by using the two scales, we were somwhat encouraged by the extent to which many respondents took the exercise in the spirit it was intended, and thought through the issue. Although analysis is not complete, we would welcome views on how useful such data might be, and whether it is worth exploring the WTA concept or WTP methods further as a means of capturing and valuing wider benefits of complex interventions.

5. Reporting of economic evaluation in context of systematic review

Assuming we can resolve the issues highlighted thus far, how best might the results of our economic evaluation be reported in light of the findings from the RCT and in the context of the concurrent systematic review?

To summarise, the intervention we evaluated showed no improvement in primary or other outcomes at 6 months compared to routine care, and the increased costs of the intervention were not off-set at that point by savings in other health and social care costs (i.e. costs in the intervention group were significantly higher than in the control). Preliminary analyses suggest that including patient and other indirect costs would not alter this conclusion. Short-term (2 month) changes in some aspects of self management in the intervention group did not translate into any differences in health outcomes at this time point, with no difference between groups in any health, behavioural or psychological outcomes at 12 months. Despite this, patients identified (primarily non-health related) benefits from the programme and reported that they would only be willing to accept relatively high payment as compensation for not having had it.

Economic evaluation is a broad framework, where the type of evaluation, method used and way in which data are reported depends on the policy question and perspective taken. Therefore, standardised checklists on the conduct and reporting of economic analyses are often resisted. However, quality of evidence and reasoning is vital to fair and honest judgement, and this principle drives initiatives such as the CONSORT (for RCTs)[28] and QUORUM (for systematic reviews)[29] statements. Recent papers in economic evaluation methods aim to achieve similar standards for conduct and presentation of economic studies[30]. If effects are not different, as is the case in our trial, then the simple advice is that the choice of intervention should be based on cost alone. More recently, however, advice has been to explore of the probability of cost effectiveness, even if the difference in key outcomes is not *statistically* significant at the conventional level[31]. The tension between the first (Frequentist/Fisherian) decision rule, and the second (Bayesian/Descriptive) approach is one we have felt in the analysis and reporting our RCT. We have not yet converted SF36 data into SF6D utilities but have the opportunity to do this to allow more complex analyses e.g. around cost-effectiveness acceptability curves. But should this still be done if there are clearly no differences, statistically significant or otherwise? It is unclear whether time should be spent on additional, specialist analyses of data from RCTs where (as a result of much time and effort) detailed costing has been undertaken but there is no difference in effectiveness results. Should we instead present a 'simple' cost-minimisation study? If not, how can data be presented to aid interpretation by decision makers?

This issue, of how to report our results, is further complicated by the need to present an up-to-date model, along the lines of that suggested by Sullivan and others[1,32], of the cost-effectiveness of psycho-educational interventions in severe asthma for the systematic review. In this case, we had to decide whether to attempt to build a model based on the collective best evidence from the review, or simply select the best estimates of cost effectiveness from the previous research. Three of the four economic studies in adults that were reviewed drew conclusions about cost effectiveness. One did not report formal economic analyses, and the trial other than our own that related costs to patient health outcomes, found a net reduction in health care costs and days lost from work plus improvements in asthma related quality of life. As highlighted above, our study found a statistically significant net increase in health care costs, and no significant difference in primary health outcomes. Assessment of study quality as per standard economic checklists (see Table 4, Appendix 2) suggested that only our own study could be considered a full cost-effectiveness analysis based on an effectiveness study of a sound design. It should be noted, however, that the other study comparing costs and health outcomes was reported as a blinded RCT, but details were only available from abstracts at the time of the review, thus it is difficult to assess methods used for the economic evaluation. The other two studies were effectiveness studies which provided some, often

very limited, planned or unplanned assessment of costs. As it turned out then, our own RCT provides the best evidence on the value of psycho-educational interventions for adults with severe asthma and the only clear recommendation is for further, good quality research in this field. It is not clear, however, how our RCT results should be interpreted and reported in light of the limited existing and poor quality evidence from the systematic review.

The CONSORT statement on reporting of RCTs[28] specifies that trial results should be reported in the context of a systematic review of all previous comparable studies, and so report on what the individual study adds to what is known. At present, however, there is no clear recommendation on whether this should also apply to economic evaluations and. whether estimates used as parameters in economic models should be based on single trial estimates or findings from systematic reviews[33]. How then should our results be presented, and the data identified used to model the likely cost effectiveness of different types of psycho-educational interventions in different patient groups[32], in order to guide decision makers?

6. Discussion

Conducting these studies of complex psycho-educational interventions has proved enlightening! As discussed, there are several important issues that we think are raised in evaluating these sorts of complex interventions, but the question now is where do we go from here?

6.1. Where do we go in evaluating complex interventions?

The primary issue, particularly given increased emphasis on the need for this type of research[34], is where we go as a research community in conducting, and developing methods for, the evaluation of complex interventions. Key in this is the applicability of current guidelines for economic evaluation[30], to complex social interventions, particularly in complex patient groups. As indicated, we do not see this as an 'asthma only' issue, and indeed at UEA we have been involved in a number of evaluations of similarly complex interventions (e.g. provision of Breakfast Clubs, home medication review, provision of day care, carer support) where comparable issues have arisen. Here we have discussed issues with respect to cost and benefit assessment and the reporting of results in light of "negative" findings and the evidence from systematic reviews. However, there are other issues, particularly with respect to interventions with children or carers, people of different socio-economic status (given this is a major determinant of resource use and access to care) and diseases of different severity. It may be that specific types or aspects of complex interventions are most cost beneficial in different groups, thus how are these groups to be effectively identified and how might analyses be conducted differently to accommodate additional issues? The key question is the extent

to which general guidelines are useful to guide the conduct and reporting of RCTs, economic evaluations and systematic reviews, and what additional recommendations may be needed (or indeed obtainable from elsewhere), in relation to complex psycho-social, lifestyle, interventions?

6.2. Where do we go in policy recommendations?

It is critical not to get too focused on the methodology for evaluation without considering the policy issue at hand. Here the key issue seems to us to be in the breadth of coverage of costs and benefits. For instance, the spill-over to social services of benefits or costs may be coming increasingly important as the move toward local 'health economies' and joint PCT/Social Services funding and work progresses. Who is the audience for the evaluation of such 'lifestyle' interventions?

6.3. Where we go in writing up the results of our trial and systematic review?

Last, but not least of course, is how best to write up our own research for publication, and whether clinical and economic data, trial and review results should be reported separately or together. It seems to us that there are a number of options: (1) report the economic evaluation results from the trial as part of a general paper on the main clinical findings or prepare two separate papers; (2) report the economic aspects of the review with the effectiveness results from the review, or write them up separately; (3) combine the economic and/or effectiveness results of the systematic review and trial; (4) prepare a paper based on the one presented and focus on the methodological issues. There are advantages and disadvantages to all of these, and we are interested in people's opinions and experience in similar situations. We would also welcome feedback and discussion on whether there is any value in developing this paper, potentially drawing on additional examples from our involvement in other studies of complex interventions, to further highlight the issues raised.

We look forward to HESG giving us the answers!

References

1. Sullivan SD, Elixhauser A, Buist AS et al. National Asthma Education & Prevention Program Working Group report on the cost-effectiveness of asthma care. *Am J Respir Crit Care Med* 1996;154:S84-S95.
2. Campbell M, Fitzpatrick R, Haines A et al. Framework for design and evaluation of complex interventions to improve health. *Brit Med J* 2000; 321:694-6.

3. Lindsay B. Randomized controlled trials of socially complex nursing interventions: creating bias and unreliability? *J Adv Nurs* 2004;45(1):84-94.
4. Donaldson C, Mugford M, Vale L (Eds). *Evidence-based health economics: from effectiveness to efficiency in systematic review*. London: BMJ Publishing Group; 2002.
5. Bousquet J. A physician's view of health economics in asthma. *European Respiratory Review* 1995; 5(30):275-8.
6. Buist AS. Cost-effectiveness of asthma management strategies. *European Respiratory Review* 1995; 5(30):292-4.
7. Bryan S, Buxton MJ. Economic evaluation of treatments for respiratory disease. *Pharmacoeconomics* 1992; 2(3):207-18.
8. Buxton MJ. Economic evaluation studies in respiratory medicine. *Respir Med* 1991; 85(Supplement B):43-6.
9. Jönsson B. A health economist's view. *European Respiratory Review* 1995; 5(30):271-4.
10. McKenzie L. *Economic evaluation in asthma care: methodological issues in measuring costs and outcomes and a review of recent studies*. (HERU Discussion Paper 4/97). Aberdeen: Health Economics Research Unit, University of Aberdeen; 1997.
11. Rutten-Van Mölken MPMH, Van Doorslaer EKA, Rutten FFH. Economic appraisal of asthma and COPD care: A literature review 1980-1991. *Soc Sci Med* 1992; 35(2):161-75.
12. National Institutes of Health. NAEPP task force on the cost-effectiveness, quality and financing of asthma care. NIH Publication No. 55-807. Washington: NIH; 1996.
13. Bartlett EE. Cost-benefit analysis of patient education. *Patient Educ Couns* 1995; 26:87-91.
14. Krahn MD. Issues in the cost-effectiveness of asthma education. *Chest* 1994; 106(4 Supplement):264s-9s.
15. Liljas B, Lahdensuo A. Is asthma self-management cost-effective? *Patient Educ Couns* 1997; 32:S97-S104.
16. Volmer T. Economic aspects of patient education programmes. *Pneumologie* 1997; 51(8):850-7
17. Lahdensuo A, Haahtela T, Herrala J et al. Randomised comparison of cost effectiveness of guided self management and traditional treatment of asthma in Finland. *Br Med J* 1998; 316:1138-9.
18. Bolton MB, Tilley BC, Kuder J et al. The cost and effectiveness of an education program for adults who have asthma. *J Gen Intern Med* 1991; 6 (Sep/Oct):401-7.
19. Sculpher, MJ, Buxton MJ. The episode-free day as a composite measure of effectiveness: an illustrative economic evaluation of formoterol versus salbutamol in asthma therapy. *Pharmacoeconomics* 1993 Nov; 4(5):345-52.

20. Richards JM, Hemstreet MP. Measures of life quality, role performance, and functional status in asthma research. *Am J Respir Crit Care Med* 1994;149:S31-9.
21. Jones PW. Quality of life, health economics and asthma. *European Respiratory Review* 1995; 5(30):279-83.
22. Blaiss MS. Outcomes analysis in asthma. *JAMA* 1997; **278**(22):1874-80.
23. Blumenschein K, Johannesson M. Relationship between quality of life instruments, health state utilities, and willingness to pay in patients with asthma. *Ann Allergy Asthma Immunol* 1998; 80:189-94.
24. McKenzie L, Cairns J, Osman L. Symptom-based outcome measures for asthma: the use discrete choice methods to assess patient preferences. *Health Policy* 2001;57:193-204.
25. Revicki DA, Leidy NK, Brennan-Diemer F et al. Integrating patient preferences into health outcomes assessment: The Multiattribute Asthma Symptom Utility Index. *Chest* 1998; 114:998-1007.
26. Dowie J. Decision validity should determine whether a generic or condition-specific HRQOL measure is used in health care decisions. *Health Econ* 2002;11:1-8.
27. Barner JC, Mason HL, Murray MD. Assessment of asthma patients' willingness to pay for and give time to an asthma self-management program. *Clin Ther* 1999; 21(5):878-94.
28. Altman DG, Schulz KF, Moher D et al. The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. *Ann Intern Med* 2001;134:663-94.
29. Moher D, Cook DJ, Eastwood S et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Lancet* 1994;354:1896-900.
30. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *Br Med J* 1996, 313: 275-283.
31. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000;17:479-500.
32. Weiss KB, Sullivan SD. The economic costs of asthma: A review and conceptual model. *PharmacoEconomics* 1993; 4(1):14-30.
33. Mugford M. Using systematic reviews for economic evaluation. In Egger M, Davey-Smith G, Altman D, eds. *Systematic reviews in health care: Meta-analysis in context.* London: BMJ Publishing, 2001; 419-28.
34. Medical Research Council. Clinical trials for tomorrow: An MRC review of randomised control trials; London: MRC; 2003. See http://www.mrc.ac.uk/current-clinical_trials_for_tomorrow/.

Appendix 1: What is known about severe asthma

- Despite effective drug treatments and management guidelines[1] a significant minority of people with asthma continues to suffer from severe or poorly controlled disease[2].
- The burden of severe asthma is most evident through its adverse consequences, such as asthma deaths, near-fatal attacks and hospital admissions[2].
- Patients with severe asthma consume a disproportionate amount of healthcare resources, incur greater personal costs and account for the majority of societal costs due to asthma[3], with 10% of patients accounting for 50% of costs and 75% of costs resulting from uncontrolled disease[4].
- Since they primarily result from acute exacerbations, most of these costs should be avoidable with adequate management[5].
- In recent years, the role of patient-related factors in contributing to severe asthma has been increasingly recognised, with significant psychological or socio-economic problems present in over 70% of patients dying from asthma[6,7,8] and experiencing near-fatal attacks[7,8,9].
- Many psychosocial factors are potentially amenable to intervention, thus "psycho-educational" programmes to address them are increasingly being implemented alongside conventional medical care.
- Reviews of studies in *general* adult samples provide some evidence that asthma self-management and related interactive educational interventions can improve health outcomes in asthma[10,11,12].
- Evidence on other types of psychotherapeutic programmes[13], multi-faceted interventions[14] and the effectiveness of psycho-educational interventions in adults with *severe asthma* [15], is sparse.
- In addition to uncertainties regarding the effectiveness of psycho-educational interventions in asthma, and severe asthma in particular, little is known about cost-effectiveness in this context[3].

1. British Thoracic Society *et al*. Guidelines for management of asthma: 1995 review and position statement. *Thorax* 1997; **52**(51 supplement):S1-S21.
2. National Asthma Campaign. Out in the open: A true picture of asthma in the United Kingdom today. *The Asthma Journal* 2001;**6**(3 special supplement).
3. Sullivan SD *et al*. National Asthma Education & Prevention Program Working Group report on the cost-effectiveness of asthma care. *Am J Respir Crit Care Med* 1996;**154**:S84-S95.
4. Barnes PJ *et al*. The costs of asthma. *Eur Respir J* 1996;**9**:636-42.
5. Blainey D et al. The cost of acute asthma - how much is preventable? *Health Trends* 1990-1; 22(4):151-3.
6. Wareham NJ *et al*. A district confidential enquiry into deaths due to asthma. *Thorax* 1993;**48**:1117-20.
7. Campbell DA *et al*. A comparison of asthma deaths and near-fatal asthma attacks in South Australia. *Eur Respir J* 1994;**7**:490-7.
8. Innes NJ *et al*. Psychosocial risk factors in near-fatal asthma and in asthma deaths. *J R Coll Physicians Lond* 1998;**32**(5):430-4.
9. Campbell DA *et al*. Psychiatric and medical features of near fatal asthma. *Thorax* 1995;**50**:254-9.
10. Clark NM, Nothwehr F. Self management of asthma by adult patients. *Patient Educ Couns* 1997; 32(Supplement):S5-20.
11. Devine EC. Meta-analysis of the effects of psychoeducational care in adults with asthma. *Res Nurs Health* 1996; 19:367-76.
12. Gibson PG *et al*. Self-management education and regular practitioner review for adults with asthma (Cochrane review). In: *The Cochrane Library*. Issue 2, 2004. Chichester: John Wiley & Sons Ltd.
13. Fleming SL *et al*. Psychotherapeutic interventions for adults with asthma (Cochrane Review). In: *The Cochrane Library*. Issue 2, 2004. Chichester: John Wiley & Sons Ltd.
14. Ram FSF et al. Primary care based clinics for asthma (Cochrane Review). In: *The Cochrane Library*. Issue 2, 2004. Chichester: John Wiley & Sons Ltd.
15. Fitzgerald JM, Turner MO. Delivering asthma education to special high risk groups. *Patient Educ Couns* 1997; 32(Supplement):S77-86.

Appendix 2: Summary of systematic review study

Methods: Standard systematic review methods[1] were used to identify, select and assess literature relevant to reviewing the content, effectiveness and cost-effectiveness of psycho-educational interventions for adults and children with severe and "difficult" asthma. Asthma terms combined with complex permutations for describing educational, self-management, psychosocial and multi-faceted interventions were used to search 32 electronic databases and guided hand-searching of reference lists, conference proceedings, current contents and three key journals. Abstracts and/or titles were assessed in duplicate against definitions developed via literature reviews and consultation at the start of the review, to identify potentially eligible interventions targeted to patients with forms of or risk factors/outcomes associated with severe asthma. Final inclusion decisions were made on the basis of viewing full text documents. Two reviewers then graded initially included studies along dimensions related to study design and relevance in terms of their degree of targeting to severe asthma patients. A third reviewer resolved disagreements or uncertainties. Descriptive, methodological and outcome data were extracted from studies meeting a minimum design and relevance threshold. Characteristics of these studies were tabulated and their results qualitatively synthesised. Where possible and appropriate, quantitative syntheses (meta-analyses) of key outcomes were also undertaken using RevMan software and a random effects approach to calculate pooled effects (e.g. relative risks [RR]).

Studies identified as reporting assessment of costs in monetary terms were included in the review of costs and cost-effectiveness. Data pertinent to describing and assessing the quality of cost and cost-effectiveness studies were extracted using a form developed on the basis of a number of existing checklists[2,3,4] and other recommendations[5,6]. Economic data were qualitatively synthesised to describe cost and resource implications of interventions, where possible considering resource consequences from different viewpoints. For comparison of costs between countries and over time, data were converted to UK pounds sterling at 2002-3 values based on OECD purchasing power parity conversion ratios[7] and annual pay and price inflation rates[8]. The simple pooling of cost effectiveness ratios from different studies has been widely criticised, mainly on the grounds of the very wide range of heterogeneity in these complex variables[9,10].

Summary results:

Quantity, type and quality of research identified

From over 23,000 "hits", after initial screening and removal of duplicates, 4,240 citations were assessed against eligibility criteria and 278 citations associated with 188 studies initially included and classified. Detailed data were extracted from 107 papers associated with 57 studies including an independent control and with at least possible targeting to severe asthma. Twenty-two of these were in adults (given the focus of this paper, details of studies in children are not reported here). Qualitative synthesis of all 22 adult studies was undertaken and six RCTs contributed data to one or more meta-analyses. Twenty of the studies had been published since 1990 and eight of these since 2000. Seven had been conducted in the US, six in the UK, five in Australia/NZ, two in other European countries and two in other countries. The classification of these studies by study design and degree of relevance is shown in Table 3.

Table3 Classification of studies in adults reviewed in depth

Targeting to difficult asthma	Randomised trials	Controlled trials	Controlled prospective observational	Controlled retrospective observational	**TOTAL**
Definite	1	0	2	0	**3 (14%)**
Probable	5	0	0	2	**7 (32%)**
Possible	8	2	1	1	**12 (55%)**
TOTAL	**14 (64%)**	**2 (9%)**	**3 (14%)**	**3 (14%)**	**22**

The studies covered a number of intervention types, involving a broad range of providers and the timing of the interventions, their delivery methods, durations, intensities, content, add-ons and settings were variable and rarely based on use of any formal psycho-educational theory or approach. The methodological quality of studies, assessed against standard criteria, was generally poor and sample sizes often small. However, there were relatively high participation (~two-thirds) and follow up rates (~80%) suggesting some success in targeting at-risk patients.

Effectiveness results

The large range of outcomes measured and their assessment and reporting in different ways across studies, precluded meta-analyses of most effectiveness data. However, of the most commonly reported outcomes there were reductions in admissions for adult studies with possible targeting to severe asthma (RR=0.57, 95% CI=0.34-0.93) but a lack of data for other groups. There was no evidence of overall effects of interventions on emergency attendances (RR=1.03, CI=0.82-1.29), and mixed results with regard to symptoms and quality of life across individual adult studies (these could not be combined). There is thus limited evidence of overall positive effects of psycho-educational interventions in adults with severe asthma and a lack of quality research, especially in the most at-risk patient groups, limits conclusions regarding effectiveness. It was not possible to draw conclusions regarding the relative effectiveness of different intervention types.

Quality of, and results from, economic studies

A total of seven of the 22 adult studies were initially tagged as economic studies and considered for economic data extraction. Economic data were ultimately extracted from four of these, including our own RCT. Two recently completed RCTs had been described as cost-effectiveness studies but could not be reviewed further as economic studies because costing methods and cost data had not been reported at the time of the review. For one further RCT separate cost data were not available for the subgroup of patients of interest. All but our own RCT were undertaken in the US and reported costs in US dollars. Only our own RCT was considered a full cost-effectiveness analysis based on an effectiveness study of a sound design. One other compared costs and outcomes in a study reported as a blinded RCT, but was reported only in abstracts at the time of the review, and thus it is difficult to assess methods used for the economic evaluation. The other studies were effectiveness studies which provided some, often very limited, planned or unplanned assessment of costs. The BMJ checklist[5] was used to identify features of the studies pertinent to an assessment of their quality and a summary of these is provided in Table 4.

Table 4 Summary of economic study quality from systematic review

Number of BMJ checklist items included	Number of studies
0-10	1
11-20	2
21-35	1
TOTAL	4

Details on the range of costs assessed in studies are provided in the main text but the table below summarises differences in health care costs in the three studies in which these could be assessed.

Table 5 Mean differences in health care costs per adult patient for economic studies

Study	Intervention	Period for costs (months)	Reported mean difference in cost per patient	Mean difference in cost per patient £ sterling 2003 prices (to nearest £10)	Comments
Mayo 1990	Vigorous medical regimen & educational programme	8	US $1900 net saving	£1910 net saving	Estimated from data provided

Zimmermann 2000	Nurse specialist education for inpatients	6	US $3480 net saving per intervention patient	£2510 net saving	Insufficient information to judge quality of economic results
Smith 2003	Specialist nurse-led home based psycho-educational programme	6 (12 planned)	£2966 (95%CI £1229-4702) increase in mean cost per patient	£2966 increase in costs (95%CI £1229-4702)	Based on adjusted comparison further analysis planned

Two studies reported a net saving in costs and our own study a net increase. Three of the four economic studies in adults that were reviewed drew conclusions about cost effectiveness. One did not report formal economic analyses, and the trial other than our own that related costs to patient health outcomes, found a net reduction in health care costs and days lost from work plus improvements in asthma related quality of life. Our study found a statistically significant net increase in health care costs, and no significant difference in primary health outcomes. No overall conclusions can thus be made on costs or cost-effectiveness, as data were very limited and the only clear recommendation is for more good quality economic research in this field.

1. Centre for Reviews & Dissemination. *Undertaking Systematic Reviews of Research on Effectiveness*. CRD Report 4 (2nd Edition). York: NHS CRD, University of York; 2001.
2. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *Br Med J* 1996, 313: 275-283.
3. Carande-Kulis VG *et al*. Methods for systematic reviews of economic evaluations for the Guide to Community Preventive Services. Task Force on Community Preventive Services. *Am J Prev Med*. 2000 Jan; 18(1 Suppl):75-91.
4. Centre for Reviews & Dissemination. *Improving access to cost-effectiveness information for health care decision making: the NHS Economic Evaluation Database.* CRD Report 6 (2nd Edition). York: NHS CRD, University of York; 2001.
5. Drummond MF et al. *Methods for the economic evaluation of health care programmes* (2nd edition). New York: Oxford University Press, 1997.
6. Gold, MR, Russell LB, Siegel JE, Weinstein MC (Eds.). *Cost-effectiveness in health and medicine.* New York: Oxford University Press. 1996.
7. OECD. OECD purchasing power parity data: Comparative Price Levels. http://www.oecd.org; 2003.
8. Hospital & Community Health Services (HCHS) Newsletter. HCHS pay and price inflation. http://www.info.doh.gov.uk/doh/finman.nsf/newsletters; 2000.
9. Jefferson T et al. An exercise on the feasibility of carrying out secondary economic analyses. *Health Economics* 1996; 5(2):155-65.
10. Mugford M. Using systematic reviews for economic evaluation. In: Egger M, Davey-Smtih G, Altman DG (Eds). *Systematic reviews in health care* (2nd edition). London: BMJ Publishing Group; 2001: 419-428.

Appendix 2: Summary of randomised controlled trial (RCT) and economic evaluation study

Methods: 92 (51%) of 180 identified adult patients with severe asthma (on the two highest treatment steps and/or having experienced previous hospital admissions for asthma), who were judged to be poorly compliant with recommended management (66% because they regularly failed to attend routine clinic appointments), agreed to participate in an RCT. This incorporated a prospective economic evaluation and was pragmatic i.e. designed to assess *in practice* the effectiveness and cost-effectiveness of an individualised psycho-educational programme delivered by a Respiratory Nurse Specialist (intervention), compared to usual care (control). Primary outcome data, comprising measures of asthma symptom control[1], generic health status (Short Form 36 Health Survey[2]) and asthma-specific quality of life (Living with Asthma Questionnaire[3]), were collected via self-completed questionnaires administered during assessment visits to patients' homes on entry to the study (baseline), and at 2, 6 and 12 months. Psychological morbidity and aspects of self-management were also assessed but are not reported in detail here. Resource use data were collected at baseline, 6 and 12 months via and interviewer-administered questionnaire and covered:

- hospital admissions, accident and emergency department attendances, ambulance use and hospital outpatient visits for asthma and other conditions over the previous 6 months;
- type and number of contacts with general practitioners, nurses, other community based staff and social services for asthma and other conditions over the previous month, plus an indication of typical contacts if the previous month was atypical;
- doses of all medications used or prescribed for use in the previous week plus an indication of typical use or recent changes if the previous week was atypical;
- any health-related equipment, devices or adaptations prescribed or loaned from health services in the previous six months;
- recent patient costs related to prescriptions, purchase of over the counter medications, equipment, adaptations, private health care, phone calls and travel to health services; and
- time off work, education or usual activities due to asthma, other illnesses or the need to attend appointments in the previous month, plus an indication of the need for any carer input.

Where necessary data were extrapolated as guided by patient reports of typicality to provide total resource usage for each 6 month period. Resource use data were then combined with unit costs obtained from published sources[4,5,6] for the study mid-point price year of 2001 to produce total health and social service costs per patient for each period. Per patient costs of the intervention were calculated as follows: the cost of the nurse time spent on patient care and costs of clinical supervision meetings for the intervention (travel and personnel costs) were divided by the total number of intervention patients and this amount added to costs obtained by combining data from the nurse's log of travel, telephone calls, letters, information and resources associated with each patient with local unit costs for these items. Patient travel, time and other indirect costs were also calculated using recommended methods[7,8]. The 6 month follow up served as the primary endpoint of the study for the statistical analyses of primary outcome and cost data. At this point, patients in the intervention and control groups were also interviewed regarding the perceived benefits of the intervention (i.e. actual and anticipated respectively). They were asked to provide a maximum of three benefits and weight these against each other given 100 points. Responses were grouped into 12 logical themes. Using a payment card showing figures from £0 to £100 (initial 26 patients) or £1m (all other patients) patients were also asked to indicate what level of payment they would be willing to accept (WTA) instead of receiving the programme and report any reasoning behind this.

Summary results: The majority of recruited patients had poor asthma control, were engaging in behaviours and using coping strategies indicative of poor self-management, had high levels of physical and psychological co-morbidities, and were living in difficult social and economic circumstances. They thus shared clinical and psychosocial characteristics with those experiencing asthma deaths, near fatal asthma and admissions in previous studies.

The intervention was, however, overall of no benefit in improving outcomes. There were no differences between intervention and control groups in primary outcomes at 6 months (see Table 6). Short-term (2 month) changes in some aspects of self management behaviour in the intervention group (in relation to reliever medication use and monitoring of peak flows) did not translate into any differences in health or other outcomes (e.g. psychological morbidity, other aspects of self management, coping) at this time point and there were no differences between groups in any outcomes at 6 and 12 months. The increased costs of providing the intervention were not off-set at 6 months follow up by any savings in other health and social care costs i.e. costs in the intervention group were significantly higher than those in the control (Table 7). Preliminary data suggest that inclusion of data on patient and indirect costs would not alter this conclusion and that there are no long term differences in costs. Despite this, patients identified (primarily non-health related) benefits from the programme and reported that they would only be willing to accept relatively high payment as compensation for not having had it –details of this are reported in the main text.

Table 6 Primary outcomes for intervention and control groups at the 6 month primary endpoint

		Control (N=39)	Intervention (N=41)	Significance*
Asthma control score†	Mean (SD)	4.05 *(2.99)*	4.27 (*3.53)*	
	95% CI	3.08 - 5.02	3.15 - 5.38	0.905
LWAQ score‡	Mean (SD)	1.06 *(0.40)*	1.02 *(0.46)*	
	95% CI	0.93 - 1.19	0.87 - 1.16	0.507
SF-36 phys func score††	Mean (SD)	54.49 *(30.15)*	52.44 *(31.78)*	
	95% CI	44.71 - 64.26	42.41 - 62.47	0.966
SF-36 ment hlth score††	Mean (SD)	65.44 *(21.18)*	67.32 *(21.33)*	
	95% CI	58.57 - 72.30	60.58 - 74.05	0.771

*p value obtained from analysis of covariance (ANCOVA) which adjusted for differences in gender and education levels between groups at baseline.
†0-9 scale, lower = better control; ‡0-2 scale, lower = better quality of life; ††0-100 scale, higher = better health status

Table 7 Total health and social services costs at the 6 month primary endpoint

Cost Items (£)		**Control (N = 39)**	**Intervention (N=41)**	***Significance****
Health & social services costs				
	Mean (SD)	£2,387.44 (£2,176.99)	£4,081.47 (£5,006.89)	
	95% CI	£1,681.74 - £3,093.14	£2,501.10 - £5,661.84	
Intervention costs	*Mean (SD)*	£0.00	£1,271.34 (£43.62)	
	95% CI		£1,257.57 - £1,285.11	
Total costs	*Mean (SD)*	£2,387.44 (£2,176.99)	£5,352.81 (£5,016.42)	
	95% CI	£1,681.74 - £3,093.14	£3,769.43 - £6,936.18	$p < 0.001$

*p value obtained from analysis of covariance (ANCOVA) which adjusted for differences in gender & education levels between groups at baseline. Raw data were transformed for analysis using a log function since they were left skewed.

1. Royal College of Physicians. *Measuring clinical outcome in asthma: a patient focused approach*. London: RCP Clinical Evaluation & Effectiveness Unit; 1999.
2. Ware JE Jnr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). *Med Care*. 1992;**30**:473-83.
3. Hyland ME *et al*. A scale for assessing quality of life in adult asthma sufferers. *J Psychosom Res* 1991;**35**:99-110.
4. PSSRU. Unit Costs of Health & Social Care 2001. Canterbury: University of Kent; 2001.
5. BMA, Royal Pharmaceutical Society of Great Britain. British National Formulary 41. London: BMA, RPSGB; 2001.
6. Department of Health. NHS Reference Costs 2001. London: DoH; 2001.
7. Ungar WJ, Coyte PC, The Pharmacy Medication Monitoring Program Advisory Board. Measuring productivity loss days in asthma patients. *Health Econ* 2000; **9**:37-46.
8. Posnett J, Jan S. Indirect Cost in Economic Evaluation: The Opportunity Cost of Unpaid Inputs. *Health Econ* 1996; 5: 13-23.