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ECONOMIC EVALUATION OF NEBULIZED MAGNESIUM SULPHATE IN ACUTE SEVERE ASTHMA IN CHILDREN

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Objectives: The aim of this study was to estimate the cost-effectiveness of nebulized magnesium sulphate (MgSO4) in acute asthma in children from the perspective of the UK National Health Service and personal social services.
Methods: An economic evaluation was conducted based on evidence from a randomized placebo controlled multi-center trial of nebulized MgSO4 in severe acute asthma in children. Participants comprised 508 children aged 2–16 years presenting to an emergency department or a children's assessment unit with severe acute asthma across thirty hospitals in the United Kingdom. Children were randomly allocated to receive nebulized salbutamol and ipratropium bromide mixed with either 2.5 ml of isotonic MgSO4 or 2.5 ml of isotonic saline on three occasions at 20-min intervals. Cost-effectiveness outcomes were constructed around the Yung Asthma Severity Score (ASS) after 60 min of treatment; whilst cost-utility outcomes were constructed around the quality-adjusted life-year (QALY) metric. The nonparametric bootstrap method was used to present cost-effectiveness acceptability curves at alternative cost-effectiveness thresholds for either: (i) a unit reduction in ASS; or (ii) an additional QALY.
Results: MgSO4 had a 75.1 percent probability of being cost-effective at a GBP 1,000 (EUR 1,148) per unit decrement in ASS threshold, an 88.0 percent probability of being more effective (in terms of reducing the ASS) and a 36.6 percent probability of being less costly. MgSO4 also had a 67.6 percent probability of being cost-effective at a GBP 20,000 (EUR 22,957) per QALY gained threshold, an 8.5 percent probability of being more effective (in terms of generating increased QALYs) and a 69.1 percent probability of being less costly. Sensitivity analyses showed that the results of the economic evaluation were particularly sensitive to the methods used for QALY estimation.
Conclusions: The probability of cost-effectiveness of nebulized isotonic MgSO4, given as an adjuvant to standard treatment of severe acute asthma in children, is less than 70 percent across accepted cost-effectiveness thresholds for an additional QALY.

Keywords: Economic evaluation, Asthma, Childhood, Magnesium sulphate

Acute severe asthma is one of the main reasons for acute hospital admission in children and is a significant predictor of morbidity, anxiety, stress, and time off school and work for children with asthma and their families (1). Recent guidelines outline criteria for the diagnosis of severe asthma in children, and recommend that initial management involves inhaled beta two ($ß_2$) agonists and ipratropium with systemic corticosteroids. For children unresponsive to initial inhaled treatment, intravenous bronchodilator therapy is recommended.

Magnesium sulphate (MgSO4) has bronchodilator effects in acute severe asthma in adults (2). Nebulized MgSO4, administered in combination with $ß_2$ agonists during adulthood, is associated with reduced hospital admissions and improved lung function (2). In contrast, the effects of nebulized MgSO4 during childhood are inconclusive (3). The Magnesium Nebuliser Trial in Children (MAGNETIC) examined the role of MgSO4 as an adjuvant to standard treatment in children (4). This study

The MAGNETIC Trial Management Group (TMG) are very grateful to all the Principal Investigators (recruitment sites and local leads listed in companion paper (4), Research Practitioners, Site Pharmacists, and participating families for their contribution, commitment and enthusiasm and to Professor Chris Butler for initial assistance with the protocol development and grant application. The MAGNETIC TMG is also grateful to the following: Hannah Short, MAGNETIC data manager; the MCRN Local Research Networks (LRNs) in England; ScotMCN in Scotland; CRC Cymru in Wales; the Trial Steering Committee (chaired by Prof Ian Russell) and the Data and Safety Monitoring and Committee (chaired by Prof David Jones) for their support and work throughout the study. This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (project number HTA 05/503/10). The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

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summarizes an economic evaluation conducted on the basis of the MAGNETIC study.

METHODS

Trial Background

MAGNETIC (ISRCTN81456894) was a prospective randomized controlled trial of 508 children aged 2–16 years with severe acute asthma (4). Participating children were recruited from emergency departments (EDs) or children's assessment units (CAUs) in 30 hospitals in the United Kingdom between January 2009 and April 2011. They received local hospital defined conventional therapy. They were randomly allocated to either nebulized salbutamol 2.5 mg (aged 2–5 years) or 5 mg (aged 6 years and over) and ipratropium bromide 0.25 mg mixed with either 2.5 ml of isotonic MgSO4 ($n = 252$) or 2.5 ml of isotonic saline ($n = 256$) on three occasions at approximately 20-min intervals. The primary clinical outcome was the Yung Asthma Severity Score (ASS) (5) at 60 min postrandomization (with MAGNETIC sized to detect a 0.5 point difference on the ASS at a 5 percent significance level with 80 percent power). Further details are reported elsewhere (4;6).

Type of Economic Evaluation, Study Perspective and Time Horizon

The economic evaluation was designed as a cost-effectiveness analysis (CEA) calculating the incremental cost per unit change in ASS, and a cost–utility analysis (CUA) calculating the incremental cost per quality-adjusted life-year (QALY) gained. The baseline economic evaluation was conducted from the perspective of the UK National Health Service (NHS) and personal social services (7). The time horizon extended to discharge from the ED/CUA or the hospital where the child was admitted to an inpatient ward immediately following ED/CUA attendance, for the purposes of the CEA, and to 1 month postrandomization for the purposes of the CUA.

Measurement of Resource Use

Data were collected about all significant resource inputs through two means. First, the MAGNETIC study captured the type, volume and duration of all resource use related to the primary ED/CAU attendance, admissions to inpatient wards, intubation, mechanical ventilation, surgical procedures, tests or investigations, additional bronchodilator medication, concomitant medications, and associated adverse events. Second, postal questionnaires completed by parents' approximately 1 month postrandomization recorded the children's resource use between completion of ED/CUA attendance or hospital discharge and one month postrandomization. These recorded use of prescribed inhalers, other prescribed medicines, privately purchased medications, community health and social services, as well as hospital outpatient attendances and hospital readmissions. These questionnaires also recorded direct nonmedical costs borne by parents and carers, and their self-reported lost earnings, as a result of attending hospital during the child's primary ED/CAU attendance and/or hospital admission(s), and as a result of the child's asthma during the follow-up period. No attempt was made to quantify, in economic terms, unpaid activities foregone by parents and carers.

Valuation of Resource Use

Unit costs for resources were obtained from a variety of sources. Unit costs for hospital and community care were largely derived from national sources and encompassed the cost of health professionals' qualifications (8). Some costs were valued using NHS Reference Costs (2009–10), a catalogue compiled by the Department of Health in England (9). Drug costs were obtained from the British National Formulary (10). Costs for individual preparations were used as well as costs for chemical entities (11). The values attached to direct nonmedical costs borne by parents and carers and their lost earnings were those provided by the parents completing the economic questionnaires. All costs were expressed in GBP (£) and valued at 2009–10 prices, and also expressed in terms of EUR (€) with currency conversions conducted through mid-year purchasing power parities. No discounting was required.

Calculation of Utilities and Quality-adjusted Life Years

Parents of children aged ≥5 years described their children's health-related quality of life at one month postrandomization using the proxy version of the EQ-5D (12). The York A1 tariff was applied to each set of responses to generate EQ-5D utility scores (13). Given methodological constraints surrounding application of the EQ-5D in young children (14), analyses were also conducted to "map" parental responses to the Asthma Module of the Pediatric Quality of Life Inventory™ (PedsQL) (15) onto EQ-5D utility scores. Mapping models were developed using data collected for 5- to 16-year-old children for whom both EQ-5D and PedsQL responses were available. These included (16): (i) an Ordinary Least Squares (OLS) model using the PedsQL total score, age, and gender as independent variables; (ii) an OLS model using the PedsQL sub-scale (asthma symptoms, treatment problems, worry, and communication) scores, age, and gender as independent variables; and (iii) an OLS model using the PedsQL sub-scale scores, squared sub-scale scores, interaction terms derived using the product of sub-scale scores, age, and gender as covariates. Further details are available elsewhere (6). The best fitting model (model (iii) (6)) was identified on the basis of its Akaike Information Criterion (AIC). This model was subsequently used to predict EQ-5D health utilities for the 2- to 4-year-old children for whom the toddler PedsQL module had been completed.

Baseline utility data was not collected within MAGNETIC because of concerns surrounding family intrusions at a sensitive time. To estimate QALYs, baseline utility data was estimated

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based on secondary evidence. A physician panel comprised of two respiratory nurses and a consultant mapped ASS scores onto EQ-5D health states from which baseline utility scores were estimated. ASS scores of 1–3 were mapped onto an EQ-5D health state of 11111; ASS scores of 4–6 were mapped onto an EQ-5D health state of 22222; and ASS scores of 7–9 were mapped onto an EQ-5D health state of 33333.

The number of QALYs accrued was calculated as the area under the baseline-adjusted (17) utility curve, assuming linear interpolation between baseline and follow-up utility scores. Given the likelihood that children return to the EQ-5D health state reported at 1 month earlier than that time, the base-case analysis assumed that the EQ-5D health state reported at 1 month was achieved immediately following hospital discharge.

Methods for Dealing with Missing Data

Multiple imputation was used to impute missing data (18). The MICE algorithm within R Version 2.13 was used to impute values for the following variables: total health and social service costs; total societal costs; QALYs based on linear interpolation assuming that the health gain was achieved immediately following hospital discharge; and QALYs based on linear interpolation assuming that the health gain was achieved linearly over the follow-up period. Age, sex, and treatment allocation were included as explanatory variables. Health service costs up to completion of ED/CUA attendance or hospital discharge was included as an additional explanatory variable in the models that imputed values for total health and social service costs and total societal costs over the 1-month time horizon. Five imputed datasets were generated.

Cost-effectiveness Analytic Methods

Datasets generated through multiple imputation were bootstrapped separately in Microsoft Excel 2003 and the results were subsequently combined (18) to calculate standard errors around mean costs and effects that incorporate uncertainty around imputed values as well as sampling variation. Standard errors were used to calculate 95 percent confidence intervals (CIs) around estimates of costs, effects and QALYs based on Student's t-distribution. Cost-effectiveness acceptability curves (CEACs) showing the probability that MgSO4 is cost-effective at a range of cost-effectiveness thresholds were generated based on the proportion of bootstrap replicates (across all five imputed datasets) with positive incremental net monetary benefits (19). For the CEA, incremental net benefit was defined as the unit reduction in ASS multiplied by its respective cost-effectiveness threshold, minus the incremental cost, where the cost-effectiveness threshold represents the maximum society is willing to pay for each unit reduction in ASS. For the CUA, incremental net benefit was defined as the incremental QALY gain multiplied by its cost-effectiveness threshold, minus the incremental cost, where the cost-effectiveness threshold represents the maximum society is willing to pay for each additional QALY. Baseline statements about cost-effectiveness assume a GBP 20,000 (EUR 22,957) per QALY gained threshold (7). The probability that MgSO4 is less costly or more effective than placebo was based on the proportion of bootstrap replicates that had negative incremental costs or positive incremental health benefits.

The following sensitivity analyses were undertaken for the CEA: (i) performing a complete case analysis; (ii) varying the per diem costs for inpatient stays in pediatric wards; (iii) assuming that part of a day spent on an inpatient ward equated to a proportional period for costing purposes; (iv) assuming that part of a day spent on an inpatient ward equated to a full day for costing purposes; and (v) varying the average cost of an ED/CUA attendance. The following sensitivity analyses were undertaken for the CUA: (i) performing a complete case analysis; (ii) assuming linear interpolation of health utilities over the 1-month follow-up period; (iii) assuming baseline ASS scores mapped onto EQ-5D health states with lower utility scores than in the baseline analysis (1–3 mapped onto health state 11222; 4–6 mapped onto health state 22333; 7–9 mapped onto health state 33333); (iv) assuming baseline ASS mapped onto EQ-5D health states with higher utility scores (1–3 mapped onto health state 11111; 4–6 mapped onto health state 22111; 7–9 mapped onto health state 33222); and (v) adopting a societal perspective.

RESULTS

The main clinical outcomes are presented elsewhere (4). In brief, children receiving MgSO4 had significantly lower ASS values after 60 min treatment (−0.25 [95 percent CI: −0.48 to −0.02]; $p = .034$) than those receiving placebo, although this did not meet the predefined clinically relevant difference of 0.5.

Resource Use and Costs

Table 1 provides a summary of resource use values. There were no statistically significant differences between the trial arms in any category of resource use with the exception of number of children who had contact with community care services (42 versus 56; $p = .033$) or who had a full blood count (30 versus 49; $p = .028$). The sources and values of relevant unit costs are summarized in Supplementary Table 1, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000440. There were no statistically significant cost differences between the trial arms in any cost category with the exception of the cost of the experimental intervention. Over the 1-month follow-up time horizon, mean total health and social service (societal) costs were GBP 1,067 or EUR 1,225 (GBP 1,157 or EUR 1,328) in the MgSO4 group, compared with GBP 1,119 or EUR 1,284 (GBP 1,202 or EUR 1,380) in the placebo group, in children with complete

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Table 1. Resource Use Values by Resource Item and Allocation Group

NHS and social care resources: from randomization to discharge Resource use based on complete case data ($N = 252$ for MgSO4 and 256 for placebo)			
	MgSO4	Placebo	*p*-value*
Initial hospital inpatient admissions	232 (92%)	245 (96%)	.097
Chest radiography	72 (29%)	83 (33%)	.386
Lung function	2 (1%)	4 (2%)	.686
Electrolytes	33 (13%)	48 (19%)	.090
Blood culture	13 (5%)	21 (8%)	.214
Full blood count	30 (12%)	49 (19%)	.028
NHS and social care resources from discharge to 4 weeks **Resource use based on complete case data ($N = 118$ for MgSO4 and 112 for placebo)**			
	MgSO4	Placebo	*p*-value*
Hospital re-admissions (asthma)	8 (7%)	8 (7%)	1.0
Outpatient visits	20 (17%)	28 (25%)	.146
Community service contacts	42 (36%)	56 (50%)	.033
Medications prescribed	51 (43%)	51 (46%)	.791
Inhalers prescribed	111 (94%)	107 (96%)	.769

Days off school

Days off school based on complete case data ($N = 89$ for MgSO4 and 80 for placebo)

	MgSO4		Placebo		Difference		
	Mean	SE*	Mean	SE	Mean	SE	*p*-value**
Full days off school	2.28	0.303	2.35	0.389	−0.69	0.488	.889
Half days off school	0.73	0.237	0.68	0.186	0.055	0.301	.855
Total days off school	2.65	0.314	2.69	3.380	−0.414	−.492	.933

*The *p*-values were calculated in SPSS using chi-square.

**Standard errors and *p*-values were calculated in Microsoft Excel/SPSS using two-tailed Student's t-tests assuming unequal variance.

cost data (Supplementary Table 2, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000440).

Cost-Effectiveness and Cost-Utility Outcomes

In the base-case CEA, the incremental cost-effectiveness of MgSO4 was estimated at GBP 189 (EUR 217) per unit decrement in ASS (Supplementary Table 3, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000440). MgSO4 had a 75.1 percent probability of being cost-effective at a GBP 1,000 (EUR 1,148) per unit decrement in ASS threshold, an 88.0 percent probability of being more effective and a 36.6 percent probability of being less costly. The cost-effectiveness outcomes remained robust to sensitivity analyses with the exception of valuing higher-level inpatient care using per diem NHS reference cost for pediatric intensive care (probability of cost-effectiveness declined to 68.3 percent). The cost-effectiveness outcomes, following multiple imputation of missing data, are summarized in Supplementary Table 4, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000440.

The results of the base-case CUA are summarized in Table 2. MgSO4 had a 67.6 percent probability of being cost-effective at a GBP 20,000 (EUR 22,957) per QALY gained threshold, an 8.5 percent probability of being more effective and a 69.1 percent probability of being less costly. The CEACs (Supplementary Figure 1, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000440) indicate that the probability that MgSO4 is cost-effective varies between 60 percent and 70 percent depending on the value of the cost-effectiveness threshold. Mean net monetary benefits associated with MgSO4 are shown in Supplementary Table 5, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000440 (GBP 63, 95 percent CI: (-219, 334), at a GBP 20,000 threshold; EUR 72, 95 percent CI: (-251, 383), at a EUR 22,957 threshold). The cost-utility outcomes remained robust to

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Table 2. Cost-Utility Outcomes for the Base-Case CUA Analysis and Sensitivity Analyses – Complete Case Analyses

	Mean costs (95% CI)			Mean QALYs gained relative to baseline (95% CI)			Probability MgSO4 is		
Analysis	MgSO4 (GBP)	Placebo (GBP)	Difference (GBP)	MgSO4	Placebo	Difference	More effective (%)	Less costly (%)	Cost-effective at a GBP 20,000 cost-effectiveness threshold (%)
Base case[1]	1056 (855, 1256)	1126 (904, 1347)	−70 (−369, 228)	0.00133 (0.00098, 0.00169)	0.00173 (0.00131, 0.00216)	−0.0004 (−0.00095, 0.00015)	8.5	69.1	67.6
Linear (U)*	1056 (855, 1256)	1126 (904, 1347)	−70 (−369, 228)	0.02530 (0.02060, 0.02999)	0.03047 (0.02539, 0.03555)	−0.00517 (−0.01209, 0.00174)	7.0	67.3	40.6
Lower (U)¶	1056 (855, 1256)	1126 (904, 1347)	−70 (−369, 228)	0.00236 (0.00198, 0.00275)	0.00268 (0.00225, 0.00312)	−0.00032 (−0.00090, 0.00026)	14.4	66.4	64.4
Higher (U)#	1056 (855, 1256)	1126 (904, 1347)	−70 (−369, 228)	0.00073 (0.00048, 0.00099)	0.00102 (0.00072, 0.00133)	−0.00029 (−0.00069, 0.00011)	7.6	69.6	68.2
Societal perspective	1145 (937, 1352)	1211 (977, 1443)	−66 (−378, 246)	0.00133 (0.00098, 0.00169)	0.00173 (0.00131, 0.00216)	−0.0004 (−0.00095, 0.00015)	8.1	64.1	63.2

[1] Complete case analysis included MgSO4 (n = 111) and placebo (n = 107).
*Linear interpolation of health utilities over the entire follow-up period, rather than assuming that the health gain was achieved immediately following hospital discharge.
¶'Lower (U)' denotes an assumption that baseline ASS scores mapped onto EQ-5D health states with lower utility scores than in the baseline analysis.
#'Higher (U)' denotes an assumption that baseline ASS scores mapped onto EQ-5D health states with higher utility scores than in the baseline analysis.

sensitivity analyses (Table 2 and Supplementary Table 5; Supplementary Figure 1) with the exception of a reduction in the probability of cost-effectiveness to 40.6 percent at a GBP 20,000 (EUR 22,957) threshold that followed linear interpolation of health utilities over the entire follow-up period. Multiple imputation reduced the probability that MgSO4 is cost effective at a GBP 20,000 (EUR 22,957) threshold to 50.9 percent (Table 3; Supplementary Figure 2, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000440). At this threshold, MgSO4 generated a mean net loss of GBP 2 (95 percent CI: -171, 168) (EUR 2; 95 percent CI: -196, 193) (Supplementary Table 6, which can be viewed online at http://dx.doi.org/10.1017/S0266462314000440). As in the complete case analysis, assuming linear interpolation of health utilities over the entire follow-up period had the largest effect on cost-utility outcomes (Table 3 and Supplementary Table 6; Supplementary Figure 2).

DISCUSSION

This study represents the first economic evaluation of nebulized MgSO4 used with standard inhaled bronchodilator therapy in acute pediatric asthma. The economic evaluation was conducted according to national methodological standards (7). The study developed novel methods for utility estimation in young children for whom validated preference-based approaches to outcomes measurement are currently lacking (14;20). It also addressed a range of methodological challenges faced by analysts conducting trial-based economic evaluations of pediatric interventions (21).

MAGNETIC demonstrated a statistically significant difference in ASS at 60 min post-treatment in favor of MgSO4, although this did not meet the predefined criterion for clinical relevance (4). Our economic evaluation found that the probability of cost-effectiveness of supplementing standard treatment of severe acute asthma in children with MgSO4 is less than 70 percent across accepted cost-effectiveness thresholds for an additional QALY. Several caveats should be noted. First, there was considerable stochastic uncertainty surrounding our cost-effectiveness estimates, which we addressed through the use of CEACs, and sensitivity analyses to handle uncertainty surrounding individual components of the economic evaluation. Second, a complete profile of resource usage, cost, and health utility data over the study time horizon was only available for 218 of 508 (42.9 percent) children, despite postal reminders to parents. In response, we applied multiple imputation techniques for handling missing values (22). Third, baseline health states were not valued using the same utility measures applied at 1-month postrandomization. Nevertheless, our sensitivity analyses revealed that our cost-utility results remained robust to alternative mapping algorithms for baseline utility estimation. Fourth, the absence of a health utility measure validated across the childhood spectrum led us to develop separate mapping algorithms between PedsQL responses and EQ-5D utility scores on the basis of data collected for 5- to 16-year-old children; the results were used to estimate EQ-5D utility scores for 2- to

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Table 3. Cost-Utility Outcomes for the Base-Case CUA Analysis and Sensitivity Analyses – Analyses Following Multiple Imputation

	Mean costs (95% CI)			Mean QALYs gained relative to baseline (95% CI)			Probability MgSO4 is		
Analysis	MgSO4 (GBP)	Placebo (GBP)	Difference (GBP)	MgSO4	Placebo	Difference	More effective (%)	Less costly (%)	Cost-effective at a GBP 20,000 cost-effectiveness threshold (%)
Base case[1]	1009 (877, 1140)	1014 (895,1131)	−5 (−181, 172)	0.00138 (0.00116, 0.00159)	0.00176 (0.00153,0.00200)	−0.00038 (−0.00070, −0.00007)	1.0	51.0	50.9
Linear (U)*	1009 (877, 1140)	1014 (895,1131)	−5 (−181, 172)	0.02458 (0.02161, 0.02755)	0.03018 (0.02709, 0.03326)	−0.00560 (−0.00988, −0.00132)	0.8	50.4	14.6
Lower (U)¶	1009 (877, 1140)	1014 (895,1131)	−5 (−181, 172)	0.00257 (0.00235, 0.00278)	0.00275 (0.00253, 0.00298)	−0.00019 (−0.00050, 0.00013)	14.2	53.0	50.6
Higher (U)#	1009 (877, 1140)	1014 (895,1131)	−5 (−181, 172)	0.00063 (0.00048, 0.00077)	0.00088 (0.00071, 0.00105)	−0.00025 (−0.00047, −0.00003)	1.6	51.4	49.6
Societal perspective	1111 (975, 1246)	1112 (987, 1236)	−1 (−185, 183)	0.00138 (0.00116, 0.00159)	0.00176 (0.00153,0.00200)	−0.00038 (−0.00070, −0.00007)	0.7	50.5	48.4

[1]Complete case analysis included MgSO4 (n = 111) and placebo (n = 107).
*Linear interpolation of health utilities over the entire follow-up period, rather than assuming that the health gain was achieved immediately following hospital discharge.
¶'Lower (U)' denotes an assumption that baseline ASS scores mapped onto EQ-5D health states with lower utility scores than in the baseline analysis.
#'Higher (U)' denotes an assumption that baseline ASS scores mapped onto EQ-5D health states with higher utility scores than in the baseline analysis.

4-year-old children. Potential alternative approaches for health utility measurement, such as parent-completed time trade-off or standard gamble exercises for all children, would have required more expensive and time-consuming data collection and were not considered practical or ethical given the acute care context. Finally, the results of our economic evaluation were particularly sensitive to the time trajectory of health gain associated with nebulized MgSO4. Future studies should pay particular attention to utility measurement during and immediately following the hospital visit or stay when the child presents with an acute episode of severe asthma.

CONCLUSION

Our study suggests that the probability of cost-effectiveness of nebulized MgSO4, given as an adjuvant to standard treatment of severe acute asthma in children, is less than 70 percent across accepted cost-effectiveness thresholds for an additional QALY. Data from our study can be used to inform future health economic studies in this area.

SUPPLEMENTARY MATERIAL

Supplementary Table 1:
http://dx.doi.org/10.1017/S0266462314000440
Supplementary Table 2:
http://dx.doi.org/10.1017/S0266462314000440
Supplementary Table 3:
http://dx.doi.org/10.1017/S0266462314000440
Supplementary Table 4:
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Supplementary Table 5:
http://dx.doi.org/10.1017/S0266462314000440
Supplementary Figure 2:
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Supplementary Table 6:
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CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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