RAACENO:

Reducing Asthma Attacks in Children using Exhaled Nitric Oxide as a biomarker to inform treatment strategy – a randomised trial

HEALTH ECONOMICS ANALYSIS PLAN

Version 1.0

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1. Background

1.1. Trial background

The search for a biomarker to guide asthma treatment has been underway for many years since current methods of assessment have major limitations, e.g. when to use which treatment, when to step down treatment. Fractional exhaled nitric oxide (FeNO) is a surrogate marker for eosinophilic airway inflammation[1–4] and, since eosinophils are seen in the airways of people with asthma[5], not unreasonably it was assumed that FeNO could be used to improve asthma control. The evidence from clinical trials, however, is that the addition of FeNO to usual care does not improve asthma control[6–8]. Whilst poor current symptomatic asthma control is certainly a risk factor for future exacerbations[9] it lacks precision, for example only 29% of children with poor asthma control on validated symptom questionnaires will have an asthma exacerbation in the following year and 8% of children with well controlled asthma will have an exacerbation (unpublished data). The confusion between exacerbation and poor symptomatic control is understandable since increased symptoms are an inevitable feature of exacerbation but most episodes of poor control are self-limiting and do not lead to exacerbation. The disconnect between symptomatic asthma control and exacerbation risk is particularly obvious in children where control is generally excellent but interrupted by exacerbations, usually in association with rhinovirus infection. Sputum eosinophilia is known to be a temporary phenomenon in children[10] and this temporality at least partly explains the poor correlation between FeNO and current and future asthma control [11–14], and also the failure of FeNO guided treatment to improve symptomatic asthma control[l6]. In contrast, changes in FeNO concentrations are more clearly seen in the context of exacerbations. For example, FeNO rises before an exacerbation[15] and falls afterwards[16]. The relationship between FeNO and exacerbation is replicated by the correlation between airway eosinophilia and asthma exacerbation; asthma treatment guided by airway eosinophilia reduces asthma exacerbations in adults[17] and children[18] (the latter with borderline significance in a small study). Of note, asthma control was not improved in either of these studies above the control arms, which were guided by a symptom-based strategy[17,18]. Eosinophilic inflammation is suppressed by treatment with inhaled corticosteroids (ICS) and FeNO increases after unsuccessful reduction[19] or cessation[20] of ICS. Together these observations show how airway eosinophilia is an index of exacerbation risk (but not of poor symptomatic asthma control) which can be suppressed with ICS and which is correlated with FeNO.

The RAACENO randomised controlled trial was designed to deliver a rigorous and adequately powered assessment of whether, in a real-world cohort and setting, FeNO guided asthma treatment prevents asthma exacerbations. It evaluates the clinical efficacy of our algorithm, and size of effect, of the intervention on asthma exacerbations while describing the relationship between FeNO, sputum eosinophilia, asthma control and exacerbations. A secondary objective of the trial was to undertake an economic evaluation of the intervention, and this document focusses on the analysis plans for this assessment. It should be read in conjunction with the study protocol.[21]

1.2 Objectives of the economic evaluation

The overall aim of the study is to compare treatment guided by FeNO and symptoms against treatment guided by symptoms alone (standard care), in children with asthma who are at risk of an asthma attack, in terms of the presence of any asthma exacerbations over 12 months requiring prescription and/or use of OCS.

The full set of objectives is provided in the study protocol. The specific economic objective is:

> To undertake an economic evaluation to assess the health care costs (e.g. asthma related hospital admissions and visits to/ from relevant health professionals, asthma medications) and other related costs (e.g. parents time of work) and quality of life effects (QALYs) of the intervention compared to routine care.

1.3 Study design and participants

Details of the study design are provided in the study protocol.[21] The RAACENO study is a multi-centred two arm parallel group randomised trial. FeNO will be measured in both arms, but only used to guide treatment decisions in the experimental arm (asthma treatment guided by symptoms and FeNO). In the control arm (asthma treatment guided by symptoms alone), FeNO will be measured, but the results will not contribute to any treatment decisions. The trial was powered to detect a relative 33% reduction in the proportion of children experiencing ≥1 exacerbation with FeNO-guided treatment compared to standard symptom guided treatment.

The trial will recruit 502 children – approximately 452 in secondary care sites across the UK, and 50 in primary care centres in Norfolk through Optimum Patient Care (OPC) or through the UK Clinical Research Networks (CRN). Clinical staff in recruiting secondary care centres will identify potentially eligible participants from medical records (both electronic and paper

based), and from clinic lists. For recruitment in primary care centres, OPC staff or other primary care or CRN staff will interrogate primary care records to identify eligible participants. Participants are to be followed up in the trial for 12 months. Clinical assessments take place at recruitment and 3, 6, 9 and 12 months afterwards.

2. Economic evaluation methods

2.1 Overview

The economic evaluation will compare treatment guided by FeNO plus symptoms with treatment guided by symptoms alone, in terms of asthma related National Health Service costs, and the number of asthma exacerbations and QALYs over a 12-month follow-up period. The analysis will rely on medication and asthma related health care resource use data collected at 3, 6, 9 and 12 months post-randomisation, and estimated incidence rates of exacerbations by treatment allocation group applied in a decision analytic modelling framework. The reported resource use data will be valued using appropriate unit costs, summed over the 12-month follow-up period for each participant, and aggregated by treatment allocation group following intention to treat principles. The mean difference in costs will be estimated for major cost categories, medication use, exacerbation related costs, and background asthma related health service costs.

A simple decision model will be developed incorporating the medication and background health care costs and the exacerbation rate and cost per exacerbation estimated from the trial data. It will be supplemented with published data on the health state utility impact of asthma exacerbations. This simple model will quantity the expected differences in cost to the health service, number of exacerbations per patient, and quality adjusted life years between the alternative treatment strategies over a 12-month period. The results will be expressed in terms of both the incremental cost per exacerbation avoided and per QALY gained for FeNO plus symptom guided treatment compared to standard symptom guided treatment. The impact of extending the time horizon to five and ten years, assuming a constant exacerbation rate, will be assessed in a secondary analysis.

A further secondary analysis will also quantify direct travel costs to participants and their parents to attend any unscheduled asthma related health care visits, and indirect costs associated with time lost from productive activities due to asthma and associated health care contacts.

2.2. Health care resource use measurement and valuation

2.2.1. Intervention cost (FeNO measurement)

In the NHS, patients with asthma undergo a "monitor and review" approach to their treatment.[22] Currently, the measurement of a patient's FeNO is not recommended in the treatment of asthma. Therefore, it will be assumed in the analysis that the intervention only incurs the cost of the extra resources required during the visit to measure and interpret the patient's FeNO in the context of the experimental treatment algorithm: the use of a reusable NIOX VERO device, cartridge for the device (which need changing after a pre-set number of measurements have been made), a single use (disposable) patient mouth filter, and any additional staff time required to carry out the test and interpret the result. The cost of the reusable device will be estimated per individual test based on the equivalent annual cost (accounting for the expected useful life span) divided by the expected annual throughput based on the average cartridge size ordered for the device by participating centres at the end of the trial period. The estimate of any additional staff time required to obtain and interpret the FeNO result will be derived from clinical opinion. Staff time will be costed using a staff cost multiplier[23] appropriate grade (band) of staff who carries out the test.

2.2.2 Background medication use

Current asthma medication use is recorded at 3, 6, 9 and 12 months, including types (and doses) of inhalers used, and doses of LTRA/Montelukast used. This data will be combined with NHS unit cost data sourced from the British National Formulary[24] to estimate the cost of preventive medication use per patient over the follow-up period.

2.2.3 Unscheduled health care contacts

Frequency of unscheduled healthcare resource use associated with asthma attacks is collected at each assessment (3, 6, 9 and 12 months) and is supported by a patient held diary. The parent fills in the follow-up case report form (CRF) retrospectively for any asthma attacks in the previous 3 months. The CRF (Section C) records information on the date, health care contacts, prescribed medicines, and the number of resource use events for each reported asthma exacerbation (section B). This data will be used to calculate a cost of all health care resource use (HCRU) associated with each asthma exacerbation. In addition, the CRF includes a section for capturing any further unplanned health care contacts for asthma or breathing problems (excluding exacerbations). This latter source of resource use data will also be costed and included in the analysis as background asthma related health care costs. All costs will be

reported in 2018/19 pounds sterling and adjustments for inflation will be made, where necessary, using the Hospital & Community Health Services (HCHS) Index and the new Health Services Index.[23]

The costing approach will assign costs to each individual component of unscheduled healthcare resource use to capture patient-level variation in costs. Unit costs for different types of unplanned health service contact are provided in Appendix 1.

For primary care contacts such as additional GP visits and community or practice nurse visits, the unit costs will be sourced from the Unit costs of Health and Social Care [23]. In addition, the cost of prescribed medications, such as oral corticosteroids, used to treat an exacerbation will be valued based on published UK unit costs.[24]

For secondary care contacts, each resource use item will be mapped to an appropriate Health Care Resource Group (HRG), where available, and costed using the relevant NHS reference cost.[25] The core HRG codes related to paediatric asthma care recorded in the CRF are PD12 (Paediatric, Asthma or Wheezing), T01 (Type 1, Emergency medicine), T03NA (Type 3 non-admitted, Emergency medicine), T04NA (Type 4 non-admitted, Emergency medicine), ASS01 (See treat or refer, Ambulance), and N08C (CHS, Specialist Nursing, Asthma and Respiratory Nursing/Liaison, Child, Face to face/Non face to face).

2.2.4 Direct costs to participants (Travel and out of pocket expenditures on medicines)

The participant time and travel questionnaire records time and travel data for a patient's most recent: emergency hospital in-patient admission, accident and emergency visit, outpatient appointment, GP appointment and out-of-hours or walk-in appointment. Travel costs will be estimated from these data based on the mode of transport reported and/or any reported fares/charges incurred. Private car journeys will be costed using the rate per mile published by HM Revenue and Customs [26], whilst NHS transportation will use the reference cost for ASS02 (See and treat and convey).[25] These participant travel costs will be assigned on a patient level basis to all unscheduled healthcare contacts associated with each asthma exacerbation over the trial period.

The follow-up CRF also records participant expenditures on any over the counter medicines, including pain killers and herbal or complimentary remedies. These costs will be included in the summation and aggregation of direct costs to participants.

2.4.5 *Indirect costs (Time lost from productive activities)*

The participant Time and Travel questionnaire records information on the time displaced from other activities when parents accessed different types of health care with their child. In addition, section F of the quarterly follow-up CRF asks about total time parents have lost from a range of productive activities because of their child's asthma. It also records the total time that children have missed from school or paid work because of their asthma since their last study visit.

To account for the time lost from productive activities, the indirect cost to society will be calculated based on the activity displaced. Gross average wage rates obtained from the Annual Survey of Hours and Earnings (ASHE), published by the Office for National Statistics,[27] will be used to value time lost from paid employment. As we do not know the age and gender of the parents for the reported time losses, a weighted average across age groups (22-59) and genders will be used. Time lost from unpaid work will be estimated using the appropriate value of unpaid work published by the Office for National Statistics.[28] The value of forgone leisure time will be estimated by multiplying time losses by the current value of non-working time available from the Department of Transport.[29]

As there is no generally accepted way of placing a monetary value on the time of children lost from full time schooling, this outcome will be reported separately in unvalued units of time.

2.3. Outcome measures for cost-effectiveness

For cost-effectiveness, the total number of exacerbations will be used as the unit of effectiveness. This represents a secondary clinical effectiveness outcome of the trial but is more suited to the cost-effectiveness analysis which should consider the cost and health impact of all asthma related exacerbations over the defined time horizon. A secondary economic analysis will also estimate the expected difference in QALYs based on the assumption that exacerbations are associated with a health state utility decrement as informed by external literature. It will be assumed that the intervention has no effect on survival and that any

difference in QALYs between arms is wholly driven by differences in the number of asthma exacerbations over the follow-up period (See section 3.4).

3. Statistical analysis of trial economic data

3.1 Aggregating and summarising costs

Resource use, costs, and health outcome data will be summarised and tabulated for comparison by treatment allocation group, following the principles of intention to treat analysis (Dummy Tables 1-2). Continuous and count variables will be presented as means (± standard deviations), and dichotomous and categorical variables will be presented as absolute numbers and percentages. All asthma related health service cost elements will be summed over the follow-up period (12-months) to estimate a total health service costs per patient. Participants costs and indirect costs will be summarised separately by intention to treat (Dummy Table 3).

3.2 Missing data

Missing cost data is a common challenge associated with trial-based economic evaluation. To estimate the total costs, complete response data for all relevant resource use variables at each follow-up timepoint point are required. Reliance on complete case data for cost-effectiveness analysis can introduce bias unless few data points are missing or data are missing completely at random. Missing data patterns and likely mechanisms for missing data will be examined. If total health service costs are missing for >10% of participants, and missing at random can be assumed, multiple imputation will be implemented using chained equations to generate multiple datasets with plausible fitted values assigned for the missing cost elements.[30] If required, the imputation model will include all of the variables in the analysis model and a number of auxiliary variables that may help to explain missingness. Rubin's rules will be used to pool estimates across the multiple imputation datasets.[31] If missing at random is judged not hold based on patterns of missing data, alternative assumptions will be explored for missing cost elements, such as applying zero values or maximal plausible values.

3.3 Analysis of cost data

The analysis of costs will be performed on an intention-to-treat basis using individual participant-level cost data. All analyses will be performed using STATA statistical software for data science (StataCorp LLC, Lakeway Drive, College Station, Texas, USA). Generalised linear regression models (GLM) with appropriate variance and link functions will be used to estimate the difference in total health service, participant, and indirect costs between the

intervention arms.[32] The models will be adjusted for minimisation factors (centre, age (<11 years; ≥11 years, sex and asthma severity (BTS Step 2, BTS Step 3, BTS Step 4)) and, if appropriate, other baseline measures that may improve the efficiency of estimation (e.g. number of admissions to hospital in last six months reported at baseline, number of days of absence from school in last six months as reported at baseline). The adjusted means and mean differences between treatment arms will be tabulated for each cost outcome by intention to treat (Dummy Table 4).

To inform the inputs for the model-based assessment of cost-effectiveness (section 3.4.), we will conduct further analyses of the trial data to inform background costs (medication and non-exacerbation related health care use) by treatment allocation, and the health service costs per exacerbation. The latter analysis will estimate the average cost of health care resource use across all exacerbations that meet the definition used for exacerbation in the trial (requiring treatment with oral corticosteroids). All other asthma related health care resource use will be incorporated as background state costs in the cost-effectiveness model.

The analysis of the number of asthma exacerbations by treatment allocation will follow the approach detailed in the statistical analysis plan and will use negative binomial regression with adjustment for baseline minimisation factors. The estimated incidence rate and rate ratio (RR) from this analysis will feed into the model-based assessment of cost-effectiveness as described below (section 3.4).

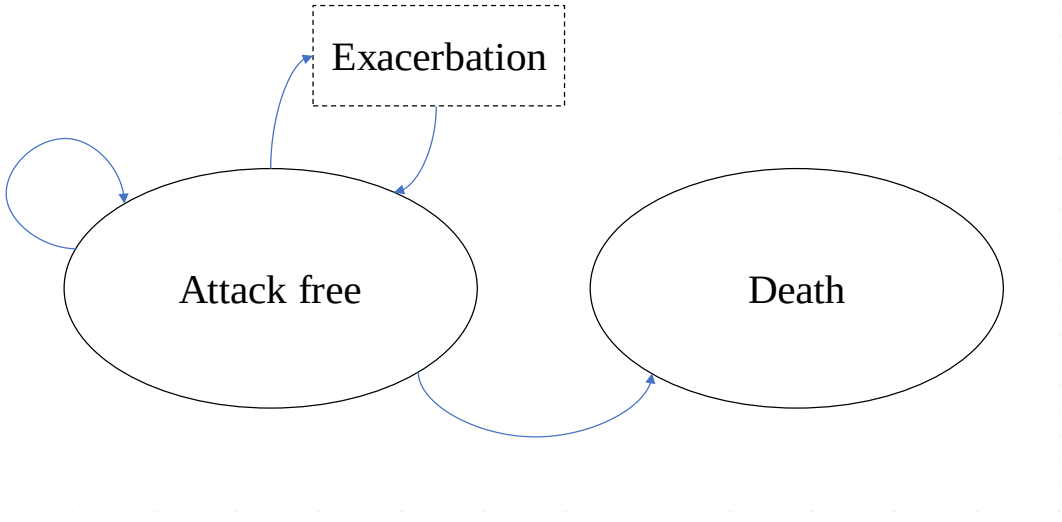
3.4. Modelling of cost-effectiveness

The cost-effectiveness analysis will utilise a simple decision model (Figure 1) to determine the incremental cost per exacerbation avoided and the incremental cost per QALY gained with FeNO plus symptom guided treatment compared to symptom guided treatment alone. The model will be informed by the trial resource use data (translated into background costs per patient per year, and the cost per exacerbation), the exacerbation rate by study arm, and published evidence on the health-related quality of life impact of asthma exacerbations.[33, 34] The model will take to the form of a simple Markov model which will utilise a two-weekly cycle in line with the exacerbation definition utilised in the trial. The utility decrements associated with asthma exacerbations will be applied for a specified duration to the expected proportion of the cohort experiencing an asthma exacerbation in each cycle of the model. Durations of asthma exacerbations of varying severity will be informed by existing literature[33,

[34] and/or clinical opinion within the study team. The utility decrements for asthma exacerbations reported in the literature differ for those requiring inpatient hospitalisation compared to those managed without inpatient admission. The applied utility decrements will be weighted by the proportion of exacerbations requiring inpatient hospitalisation as observed in RAACENO.

The model will be used to estimate expected costs, numbers of exacerbations, and QALYs over the observed time horizon of the trial in the first instance, but we will also explore the impact of extending the time horizon to five and ten years, assuming a constant incidence rate for exacerbations by treatment arm. Results will be presented in terms of the both the incremental cost per exacerbation avoided, and the increment cost per QALY gained, using the modelled expected differences in costs, exacerbations and QALYs between treatment arms (Dummy Table 5). Probabilistic sensitivity analyses will be used to characterise the uncertainty surrounding the model-based estimates of cost-effectiveness, with results displayed graphically using cost-effectiveness planes and cost effectiveness acceptability curves.[35] The variance for each cost input parameter will be derived from the analysis of the trial data described in Section 3.3. The variance surrounding the health state utility decrement of an exacerbation will be taken from the literature. Further deterministic sensitivity analysis will be conducted as necessary to explore the impact of uncertainty relating to the costing methodology (e.g. availability of alternative unit costs for key resource use events) and any further required assumptions which become apparent during the analysis.

Figure 1: Schematic of the proposed decision model



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Dummy Tables

Dummy Table 1 Health service resource use by treatment allocation

Resource use variable	**FeNO plus symptom guided treatment**	**Symptom guided treatment**
No. clinical assessments		
4; n(%)		
3; n(%)		
2; n(%)		
1; n(%)		
0; n(%)		
No. exacerbations; mean (SD)		
Unplanned primary care/community care usage; mean (SD)		
GP contacts		
Community nurse contacts		
NHS 24; NHS 111		
Out of hours GP service		
Walk in centre		
Unplanned secondary care usage; mean (SD)		
Accident and emergency (non-admitted)		
Accident and emergency (admitted)		
Other contacts		

Dummy Table 2 Health service costs by Treatment allocation

Cost variable	**FeNO plus symptom guided treatment**	**Symptom guided treatment**
Clinical assessment costs (including FeNO measurement)		
Preventive medications costs; mean (SD)		
Unplanned primary care/community care costs; mean (SD)		
GP contacts		
Community nurse contacts		
NHS 24; NHS 111		
Out of hours GP service		
Walk in centre		
Unplanned secondary care costs; mean (SD)		
Accident and emergency (non-admitted)		
Accident and emergency (admitted)		
Other contacts		
Exacerbation related medication costs; mean (SD)		
Total health service costs; mean (SD)		
Total background costs; mean (SD)		
Cost per exacerbation; mean (SD)		

Dummy Table 3 Participant costs and indirect costs by treatment allocation

Cost variable	**FeNO plus symptom guided treatment**	**Symptom guided treatment**
Direct participant/family costs; £ mean (SD)		
Travel costs		
Out of pocket costs		
Total direct participant costs		
Time displaced (participant); mean (SD)		
Hours lost school		
Hours lost paid employment		
Time displaced (parents); mean (SD)		
Hours lost paid employment		
Hours lost unpaid work		
Hour lost Leisure		
Indirect costs (participant); £ mean (SD)		
Hours lost paid employment		
Indirect costs (participant); £ mean (SD)		
Hours lost paid employment		
Hours lost unpaid work		
Hour lost Leisure		
Total Indirect costs		

Dummy Table 4 Adjusted differences in costs

Cost category	**FeNO plus symptom guided treatment**	**Symptom guided treatment**	**Difference (95% CI)**
Direct health service costs			
Preventive medications costs			
Background resource use costs			
Exacerbation related costs			
Total health service costs			
Total direct participant costs			
Total indirect costs			

Dummy Table 5 Incremental cost-effectiveness analysis

Comparator	**Total health service cost (£ mean)**	**Difference in cost (£ mean)**	**Total number of exacerbations (mean)**	**Difference in exacerbations (mean)**	**Total QALYs (mean)**	**Difference in QALYs (mean)**	**Incremental cost per exacerbation avoided (£)**	**Incremental costs per QALY gained (£)**
Symptom guided treatment		-		-		-	-	-
FeNO plus symptom guided treatment								

Appendix 1: Tables of unit costs for valuation of health care resource use

Reference cost details* - non-elective short stay (2018/19)

Currency code	Currency description	Number of FCS's	National Average Unit Cost
PD12A	Paediatric, Asthma or Wheezing, with CC score 4+	828	£740
PD12B	Paediatric, Asthma or Wheezing with CC Score 1-3	9,791	£620
PD12C	Paediatric, Asthma or Wheezing, with CC score 0	11,697	£562
Weighted average across all non-elective short stay admissions			£594.05

*https://improvement.nhs.uk/documents/6486/2_-_National_schedule_of_NHS_costs_V2.xlsx

Reference cost details* - non-elective long stay (2018/19)

Currency code	Currency description	Number of FCS's	National Average Unit Cost
PD12A	Paediatric, Asthma or Wheezing, with CC score 4+	560	£2787
PD12B	Paediatric, Asthma or Wheezing with CC Score 1-3	3,376	£1989
PD12C	Paediatric, Asthma or Wheezing, with CC score 0	2,705	£1771
Weighted average across all non-elective long stay admissions			£1967.47

*https://improvement.nhs.uk/documents/6486/2_-_National_schedule_of_NHS_costs_V2.xlsx

Reference cost details* - Day case (2018/19)

Currency code	Currency description	Number of FCS's	National Average Unit Cost
PD12A	Paediatric, Asthma or Wheezing, with CC score 4+	271	£428
PD12B	Paediatric, Asthma or Wheezing with CC Score 1-3	1,186	£372
PD12C	Paediatric, Asthma or Wheezing, with CC score 0	913	£413
Weighted average across all day case admissions			£393.87

*https://improvement.nhs.uk/documents/6486/2_-_National_schedule_of_NHS_costs_V2.xlsx

Episode trim-points of reference costs (2018/19) *

Currency code	Currency description	Non-elective spell trim point (days)	Episode trim point
PD12A	Paediatric, Asthma or Wheezing, with CC score 4+	8	5
PD12B	Paediatric, Asthma or Wheezing with CC Score 1-3	5	5
PD12C	Paediatric, Asthma or Wheezing, with CC score 0	3	3

*https://digital.nhs.uk/services/national-casemix-office/downloads-groupers-and-tools/costing---hrg4-2018-19-reference-costs-grouper

Reference cost details * - Non-admitted emergency department attendances(2018/19)

Currency code	Currency description	Severity of asthma exacerbation (% Proportion)[a]	Treatment[b]	National Average Unit Cost
VB09Z	Emergency medicine, category 1 investigation with category 1-2 treatment (type 1 non-admitted)	Moderate (100%)[c]	IV, guidance advice, inhaler via spacer for short acting beta agonist (salbutamol), oral prednisolone	£133

* https://improvement.nhs.uk/documents/6486/2_-_National_schedule_of_NHS_costs_V2.xlsx

[a] Based upon method used in table S3.7 Franklin et al. (2018)

[b] Validated by RAACENO trial clinical expert

[c] Assuming all patients who present to the emergency department with a moderate exacerbation would not be admitted

Reference cost details * - Admitted emergency department attendances (2018/19)

Currency code	Currency description	Severity of asthma exacerbation (% Proportion)[a]	Treatment[b]	National Average Unit Cost
VB06Z	Emergency medicine, category 1 investigation with category 3-4 treatment (type 1 admitted)	Severe (62.5%)[c]	Inhaler via spacer for short acting beta agonist (salbutamol), supplemental oxygen, oral prednisolone	£232
VB04Z	Emergency medicine, category 2 investigation with category 4 treatment (type 1 admitted)	Life-threatening (37.5%)[c]	IV cannulation, nebulisation, guidance advice, vital signs monitoring, supplemental oxygen, administration of infusion.	£318
Weighted average of all A&E attendances using estimated proportions of asthma severity^ presenting to hospital				£264.25

* https://improvement.nhs.uk/documents/6486/2_-_National_schedule_of_NHS_costs_V2.xlsx

[a] Based upon method used in table S3.7 Franklin et al. (2018) (Where a ratio of 5:3 of Severe to Life-threatening exacerbations present to the emergency department)

[b] Validated by RAACENO trial clinical expert

[c] Assuming all patients who present to the emergency department with a severe or life-threatening exacerbation will be admitted

Unit costs of health care resource use - Scheduled and unscheduled care

Resource use	Type of contact		Unit cost	Source
GP	Visit to surgery		£39.65	PSSRU 2019[a] (£4.30 per minute of staff time at average consultation length of 9.22[b] minutes)
	Home visit		£138.86	PSSRU 2010[b] (Inflated to 2019 prices[a] (assumes 12-minute travel time))
	Phone		£23.22	PSSRU 2019[a] (£4.30 per minute of staff time at average phone consultation length of 5.4[c] minutes)
Community asthma nurse	Visit to surgery		£12.91	PSSRU 2019[a] (£84 per hour of patient contact of band 6 GP nurse at average Nurse consultation visit length of 9.72[c] minutes)
	Home visit		£23.14	PSSRU 2010[b] (Inflated to 2019 prices)[d]
	Phone		£7.97	PSSRU 2019[a] (£84 per hour of patient contact of band 6 GP nurse at average nurse phone consultation length of 5.69[c] minutes)
Asthma clinic	Visit	Consultant	£267	NHS reference costs 2018/19, CL WF01C, Non-admitted Face-to-Face attendance, Follow-up. Community Paediatrics.
			£204	NHS reference costs 2018/19, CL WF01C, Non-admitted Face-to-Face attendance, Follow-up. Paediatric Respiratory Medicine.
		Nurse	£133	NHS reference costs 2018/19, CHS NURS N08CF F2F, Child, Specialist Nursing, Asthma and Respiratory Nursing/Liaison, Child, Face to face

	Phone	Consultant	£105	NHS reference costs 2018/19, CL WF01C, Non-admitted Non-Face-to-Face attendance, Follow-up. Paediatric Respiratory Medicine.
		Nurse	£24	NHS reference costs 2018/19, CHS NURS N08CF, Child. Specialist Nursing, Asthma and Respiratory Nursing/Liaison, Child, Non face to face.
NHS 24/ 11 service			£12.96	£12.26[d] inflated to 2019 prices using the PSSRU inflation indices[a].
Out-of-hours GP service			£74.02	Weighted average of T03A & T03NA (excluding emergency dental), NHS reference costs 2018/19.
Walk in centre			£45.71	Weighted average of T04A & T04NA (excluding emergency dental), NHS reference costs 2018/19.
Ambulance	See & treat		£209	ASS01, NHS reference costs 2018/19.
	See & convey		£257	ASS02, NHS reference costs 2018/19
Home rescue pack			£11.16	Course of 40mg/day of Prednisolone for 5 days. (Paediatric Formulary Committee. British National Formulary. (2020). Available at: https://bnfc.nice.org.uk/ (Accessed: 24 August 2020)
Pharmacist			£6.82	Cost of 9.22 minutes of band 6 community-based scientific and professional staff [a]

[a] Curtis, Lesley A. and Burns, Amanda (2019) Unit Costs of Health and Social Care 2019. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/ (Accessed: 24 August 2020)

[b] Curtis, Lesley A. (2010) Unit Costs of Health and Social Care 2010. https://www.pssru.ac.uk/pub/uc/uc2010/uc2010.pdf (Accessed: 11 September 2020)

[c] Hobbs R., Bankhead C., Mukhtar T, Stevens S., Perera-Salazar R., Holt T. and Salisbury C. Clinical workload in UK primary care: a retrospective analysis of 100 million consultations in England, 2007-14. *Lancet* 2016; **387**: 2323-30. https://doi.org/10.1016/S0140-6736(16)00620-6

[d] Pope C., Turnbull T., Jones J., Prichard J, Rowsell A. and Halford S. Has the NHS 111 urgent care telephone service been a success? Case study and secondary data analysis in England. *BMJ Open* 2017; **7**:e014815. doi: 10.1136/ bmjopen-2016-014815