Economic Plan

This document identifies the priorities for economic analysis and the proposed methods for addressing these questions as described in section 7 of the guidelines manual (2014).

1 Guideline

Full title of guideline: **Asthma: The management of asthma** (short: Asthma management)

2 Process for agreement

The economic plan was prepared by the guideline health economist in consultation with the rest of the National Centre for Clinical Guidelines (NCGC) technical team and the Guideline Committee. It was discussed and agreed on by the following people[a]:

For the NCGC and Committee:

NCGC economist(s):	Alexander Haines, Senior Health Economist
	Peter Rouse, Health Economist
NCGC representative(s)[b]:	Bernard Higgins, Guideline Lead
Committee representative(s)[c]:	John Alexander, Chair

For NICE (completed by NICE):

CCP lead:	Sarah Willett
Commissioning manager:	Caroline Keir
Economic lead:	Paul Crosland
Costing lead:	TBC

Proposals for any changes to the agreed priorities will be circulated by email to this group. If substantive revisions are agreed, they will require to be recorded as addenda to this document (section 8) or as an updated version of the document.[d]

[a] This may be done by face-to-face meeting, teleconference, or email as convenient.

[b] This may be the project manager, a systematic reviewer or research fellow and/or the centre director or manager, as appropriate for the developer and guideline. For the NCGC it will usually be the guideline lead.

[c] This may be the Committee chair, clinical lead or other members as appropriate.

[d] In case clinical questions are changed, for example, section 3 requires updating as well as other sections if modelling priorities are affected.

3 Topic priorities identified in the Scope

This section contains all topics, or clinical review questions as covered by the scope. These topics usually reflect selected clinical issues. Please indicate if an area is relevant for economic consideration and if modelling is deemed appropriate to address it.

Area[e]	Relevant?[f]	Appropriate for modelling?[g]
Pharmacological management of chronic asthma In children, young people and adults with asthma who are treatment-naïve, what is the most clinically and cost effective initial therapy to be started on: - reliever therapy alone (SABA) or, - both reliever and preventer therapy (SABA and a preventer such as ICS)	Yes	Initial scoping search found no economic or clinical evidence for the subject area. Unit costs will be presented to the GC however a research recommendation will be the most likely course of action. This question has a **low priority** for original economic analysis.
What is the most clinically and cost effective preventer drug (class or combination of drug classes) for the management of children, young people and adults with asthma who are uncontrolled on SABA alone (preventer-naïve) or who are treatment-naive?	Yes	The question is economically important as the asthma population is large meaning any change in the cost per patient will have a large impact on the NHS. Cost-effectiveness has not been reviewed in related guidelines, such as the BTS/SIGN guideline, and could therefore lead to a change in current practice and standardisation of optimal treatment. An economic model would be built on the results of the proposed network meta-analysis (NMA), allowing the whole pharmacological pathway to be modelled. Although the current economic literature may have assessed the cost-effectiveness of one treatment compared to another we do not expect to find any economic analysis which compares all relevant comparators together. Likewise it is unlikely that any existing analysis will
What is the most clinically and cost effective drug (class or combination of drug classes) for the management of children, young people and adults with asthma who are currently taking an optimal single preventer (see previous question) when this fails to provide adequate control?	Yes	
What is the most clinically and cost effective drug (class or combination of drug classes) for the management of children,	Yes	

[e] This corresponds to the 'Key clinical issues that will be covered' section in the scope or, if available, clinical review questions.

[f] Please state if this area is deemed relevant for considering opportunity costs and likely disinvestments. Areas might pose a decision problem directly, or implicitly inform the choice between options. Categories should include information on relevance and if of high or low priority for health economic work (see below).

[g] Health economic work comprises of literature reviews, qualitative consideration of expected costs and effects or formal decision modelling. Decision modelling is particularly useful where it can reduce uncertainty over cost effectiveness or where a recommendation is likely to result in considerable changes in health or costs. For further details please see section 7 of the guidelines manual (2014). It may not be feasible or efficient to address every relevant decision problem by original work. The rationale for choosing areas for cost-effectiveness modelling should be discussed in detail in sections 3 and 4.

young people and adults with asthma who are currently taking optimal preventer therapy according to step 3 (see previous question) when this fails to provide adequate control?		be based on a NMA that incorporates all the direct and indirect evidence. This question has a **high priority** for original economic analysis. Any cost-effectiveness evidence that compares two relevant comparators will be assessed and used to evaluate the consistency of our model's results.
In children, young people and adults with asthma on ICS preventer therapy, is intermittent ICS more clinically and cost effective than regular ICS?	Yes	One concern with asthma management is the unnecessary use of medication, given the known side effects of steroids. This question seeks to answer whether intermittent use of ICS, which involves using medication when required, is a better strategy than taking the same medication on a regular basis. As intermittent use involves lower medication usage, if the clinical review finds it produces the same or better health outcomes then it can be assumed to be a 'dominant' strategy, providing the same or higher health outcomes at a lower cost. If this is the case then this question could be answered without the need for detailed economic modelling. If the clinical evidence finds that intermittent use leads to more exacerbations then modelling this could be tricky. The two main benefits of intermittent use are the cost savings from lower medication use and a reduction in the adverse effects of steroids. Both of these parameters are very difficult to quantify. Medication use would vary from person to person and would be very difficult to accurately calculate. Adverse effects of steroids include stunted growth in children but the extent to which the steroid reduction would affect this and the disutility to apply to this would be very difficult. Therefore this question has a **low priority** for original economic analysis.
What is the clinical and cost-effectiveness of stepping down treatment in children, young people and adults who are controlled/stable on current therapy?	Yes	Currently it is believed that there is too much emphasis on stepping up treatment. Therefore this means that a lot of people may be over treated. If stepping down treatment can be achieved with a minimal impact on health outcomes then it will likely be a dominant economic strategy, reducing

		costs and leaving health outcomes unchanged. If this is the case then no detailed economic modelling would be necessary. If health outcomes do decrease slightly, a health economic analysis could assess if giving up these health benefits could be justified by the resources saved which could be redeployed by the NHS to achieve higher health benefits. Therefore this question has a **medium priority** for original economic analysis.
Non-pharmacological management of chronic asthma What are the most clinically and cost effective strategies to improve medicines adherence in children, young people and adults with asthma who are non-adherent to prescribed medicines?	Yes	It is believed that a significant proportion of individuals with asthma are non-adherent to their medication. This results in poorer health outcomes and unnecessary stepping up of treatment meaning it reduces health outcomes and increases costs to the NHS. It is unlikely that a study would report all the outcomes needed to perform a detailed original economic analysis. A study would need to have long term (>6 months) outcomes that looked at impact on exacerbations and quality of life. Therefore this question has a **low priority** for original economic analysis.
What is the clinical and cost effectiveness of delivering asthma care stratified according to risk of asthma attacks to improve outcomes for children, young people and adults with asthma?	Yes	Stratifying according to risk is concerned with the access to care a patient receives based on their symptoms and risk. This looks at degree of control and risk of exacerbations and allocates care accordingly. The focus of the question is around the appropriate allocation of asthma care, such as GP visits, linked to clinical outcomes. The GC felt that there is unlikely to be a large selection of clinical studies on the subject however that stratifying according to risk could have a large impact on current practice. This question has a **high priority** for original economic analysis.
What is the clinical and cost effectiveness of supported self-management (including self-management education, self-monitoring and a personalised asthma action plan, PAAP) in	Yes	The economic review identified one potentially includable study that evaluated the cost-effectiveness of self-management plans using a within-trial analysis.[1] Therefore it is possible this question can be

comparison to standard care (asthma review only), for improving outcomes for children, young people and adults with asthma in primary care?		answered without detailed economic modelling. However the GC felt there would be a large clinical evidence base to inform this question and therefore the results from one study would perhaps not be sufficient if there were conflicting results across studies. This question has a **medium priority** for original economic analysis.
What is the optimal increase in preventer therapy within supported self- management when control is lost?	Yes	The focus of this question is around the doses recommended in self-management plans. Higher dosage recommendation would result in higher costs and therefore the question is of economic importance. However it is unlikely there would be a strong clinical evidence base for this question to inform an economic model. This question has a **low priority** for original economic analysis.
Are breathing exercises clinically and cost effective for children, young people and adults with asthma?	Yes	No economic evidence has been found on this question. Threshold analysis was undertaken using the clinical evidence. The threshold analysis had a high level of uncertainty and used very low quality clinical evidence. It is not seen as feasible to conduct original economic analysis for this question, due to a lack of good quality clinical evidence. This question has a **low priority** for original economic analysis.

4 Planned modelling

This section will specify modelling work prioritised by the Committee. It will provide details on how cost effectiveness will be considered for relevant, prioritised clinical areas or decision problems. Proposed modelling work should be listed in chronological order. For each decision model, please state the proposed analytical methods, including the populations, interventions and comparators, outcomes, perspective and type of economic analysis. In addition, include relevant references and any comments and justifications on, for example, possible diversions from the NHS and PSS reference case.

Area[h] (clinical question(s)[i])	*Outline proposed analysis*
In children, young people and adults with asthma who are treatment-naïve, what is the most clinically and cost effective initial therapy to be started on: - reliever therapy alone (SABA) or, - both reliever and preventer therapy (SABA and a preventer such as ICS) What is the most clinically and cost effective preventer drug (class or combination of drug	In the model there are three main outcomes that affect costs and quality of life: 1. Exacerbations 2. Quality of life (level of asthma control) 3. Mortality The data informing these outcomes will be collected from a network meta-analysis for questions concerning the pharmacological management of asthma. The network-meta analysis should identify evidence for each step of treatment comparing all relevant comparators to enable us to populate the model. With this information, data on exacerbations and quality of life will feed into a model supplemented by costs from the NHS drug tariff for different treatment combinations and NHS reference costs for exacerbations. The model would be a Markov model with four states: no exacerbation, non-hospitalised exacerbation, hospitalised exacerbation and dead. In the 'no exacerbation' state after each cycle there would be a probability that the individual experiences an exacerbation, this could either be hospitalised or non-hospitalised. This probability would be treatment-related and be based on the clinical evidence taken from the NMA. The exacerbation would either be hospitalised leading to a high disutility and hospitalisation or non-hospitalised which would result in a smaller disutility and a lower cost, as this can be managed with oral steroids alone. The proportion of hospitalised and non-hospitalised exacerbations will be based on evidence from the clinical review. If this evidence is not available from the NMA then the proportion of severe to non-severe exacerbations will be taken from epidemiological studies and it will assumed this is the same across all treatments. Disutility values for exacerbations will be taken from Llyod et al.[2]

[h] This should be the key areas relevant for considering opportunity costs and high priority for original modelling, as identified in section 3.

[i] Two or more questions may be addressed by a single analysis if appropriate.

classes) for the management of children, young people and adults with asthma who are uncontrolled on SABA alone (preventer-naïve) or who are treatment-naive? What is the most clinically and cost effective drug (class or combination of drug classes) for the management of children, young people and adults with asthma who are currently taking an optimal single preventer (see previous question) when this fails to provide adequate control? What is the most clinically and cost effective drug (class or combination of drug classes) for the management of children, young people and adults with asthma who are currently taking	A quality of life value would be attached to the 'no exacerbation' state based on evidence from the NMA. Depending on how the data in the clinical studies is presented there may be scope to expand the model to have more states, separating the 'no exacerbation' state into controlled and uncontrolled asthma. This strategy has been employed in previous economic assessments of asthma treatment strategies. If EQ-5D data is unavailable from the clinical review then we would look into mapping data onto EQ-5D from AQLQ (asthma-quality of life questionnaire) for example. If mapping using published algorithms is not an option then we would explore attaching quality of life to states using published sources on how quality of life affects asthma control. This would involve a number of assumptions and therefore would undergo robust sensitivity analysis. There is one study by McTaggart et al[3] which attaches an EQ-5D value to fully controlled, controlled, partially controlled and uncontrolled asthma. This will give us, at a minimum, a reference on what quality of life values would be appropriate and a range of plausible values to consider for sensitivity analyses. A recently published systematic review also looks at asthma quality of life across different levels of control which may be of use.[4] One thing to note is that if an individual exacerbates then they are likely to receive a lower quality of life score anyway. Therefore adding an additional quality of life decrease every time an exacerbation occurs may overestimate the benefit of treatments that reduce exacerbations. However many of the quality of life questionnaires, such as EQ-5D, specifically ask the respondent how they feel on that particular day. Therefore they will not capture the disutility from exacerbations. This issue will be explored in sensitivity analyses. Finally mortality would be incorporated into the model using data from the clinical review. However, given the rarity of asthma related deaths and the size of the population, it may be the case that the clinical studies identified will not be sufficiently powered to account for mortality. One way to incorporate mortality would be to attach a mortality value to exacerbations. Using epidemiological studies we could calculate the probability of death associated with exacerbations. Therefore in the model when the individual exacerbates there would be a probability attached to this that would lead to death. This would therefore assume that treatments with lower exacerbation rates would lead to fewer deaths. This could only be incorporated in the absence of mortality data from the studies as it would lead to double counting. For pharmacological management the individual would move up treatment steps if the current line of therapy failed. In this sense 'failing' means that the therapy is not improving symptoms. The likelihood that a treatment was working would likely be apparent not long after the individual started taking the treatment. In this sense the 'treatment' failure would be a once occurring event as the model started rather than an on-going probability. Therefore when the model starts there will be a probability that the individual does not respond to the treatment and therefore moves on to the next treatment step. When this occurs the individual would move up a treatment step and the Markov model outcomes and probabilities would change to be in line with what is associated with the new, higher treatment step.

optimal preventer therapy according to step 3 (see previous question) when this fails to provide adequate control?

The probability of the line of therapy failing would be based on evidence from the clinical studies and would not be an outcome that would appear in the NMA. Therefore this would require extensive sensitivity analysis to ensure our results were robust. For this method to work first of all the cost-effectiveness of the final-line of therapy would be considered, as the cost-effectiveness of this would not be impacted by anything that preceded it and there is no therapy for the individual to move on to. Then once this is established the cost-effectiveness of the penultimate line of therapy would be considered and so on.

This model structure is similar to other asthma model's that have appeared in the literature in the past. These previous model's tend to have separate Markov states for level of control. However as they tend to be based on a single RCT this data is available. As we are pooling data across such a large body of evidence modelling in such a detailed way would unlikely be possible without very tenuous assumptions. However these options will be explored.

Comparators for the pharmacological review question will include:

GINA (adult)	low dose	medium dose	high dose
beclometasone diproprionate (CFC)	200-500ug	>500-1000ug	>1000ug
beclometasone diproprionate (HFA)	100-200ug	>200-400ug	>400ug
budesonide (DPI)	200-400ug	>400-800ug	>800ug
ciclesonide (HFA)	80-160ug	>160-320ug	>320ug
fluticasone (DPI)	100-250ug	>250-500ug	>500ug
fluticasone (HFA)	100-250ug	>250-500ug	>500ug
mometasone furoate	110-200ug	>220-440ug	>440ug
triamcinolone acetonide	400-1000ug	>1000-2000ug	>2000ug

GINA (children)	low dose	medium dose	high dose
beclometasone diproprionate (CFC)	100-200ug	>200-400ug	>400ug

beclometasone diproprionate (HFA)	50-100ug	>100-200ug	>200ug
budesonide (DPI)	100-200ug	>200-400ug	>400ug
budesonide (nebules)	250-500ug	>500-1000ug	>1000ug
ciclesonide (HFA)	80ug	>80-160ug	>160ug
fluticasone (DPI)	100-200ug	>200-400ug	>400ug
fluticasone (HFA)	100-200ug	>200-500ug	>500ug
mometasone furoate	110ug	≥220-≤440ug	≥440ug
triamcinolone acetonide	400-800ug	>800-1200ug	>1200

Costs and health outcomes will be discounted at 3.5%.

As mortality is an outcome, a lifetime time horizon will be used.

Probabilistic sensitivity analysis will be used to take into account uncertainty around input point estimates e.g. using standard errors. One-way / scenario sensitivity analyses will be used to explore how uncertainty about key assumptions or alternative data sources impact results. These will include setting the QALY and cost discount rate to 1.5%.

All other review questions.	For other review questions, if the clinical reviews provide evidence on exacerbations, quality of life or mortality then these values could be incorporated into the above model, changing the interventions compared and their costs. Therefore this model structure could be used for multiple review questions.

5 Clinical Guidelines Technical Support Unit[j]

Please indicate if any of the analyses or areas suggested in section 3 require or would benefit from the Clinical Guidelines Technical Support Unit support or validation.

The network meta-analysis used to inform the economic model may need support and validation from the TSU.

6 Data access

Please indicate whether the feasibility of any of the analyses or areas suggested in section 3 will be dependent on access to data sources not publicly available, and how these will be accessed, for example, through a call for evidence.

All data needed should be publically available.

7 References

1. van der Meer, V., et al. (2011). Cost-effectiveness of internet-based self-management compared with usual care in asthma: e27108.

2. Lloyd, A., et al. (2007). "The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK." Primary Care Respiratory Journal 16(1): 22-27.

3. McTaggart-Cowan, H. M., et al. (2008). "The validity of generic and condition-specific preference-based instruments: The ability to discriminate asthma control status." Quality of Life Research 17(3): 453-462.

4. Einarson, T. R., et al. (2015). "Utilities for asthma and COPD according to category of severity: a comprehensive literature review." Journal of Medical Economics 18(7): 550-563.

8 Addenda to economic plan

Please state any changes that have been made to the above agreed plan, together with date. If clinical questions have changed since the economic plan was signed off, include a new list with all clinical questions as part of the addendum, together with a comment where questions were inserted, deleted or altered and an explanation.

Scope area[k] (clinical question(s)[l])	*Proposed changes*	*Date agreed*

[j] The clinical guidelines technical support unit provides academic support to guideline developers at any point in guideline development: conduct, or support the developer team in the development of advanced evidence synthesis, support complex economic analyses, conduct validation of or amendments to existing evidence syntheses used in guideline models and address concerns from stakeholder (via consultation). Please contact the senior technical adviser for further details.

[k] This should be the key area(s) relevant for considering opportunity costs and high priority for original modelling, as identified in section 3.

[l] Two or more questions may be addressed by a single analysis if appropriate.
