EstablishINg the best STEp-up treatments for children with uncontrolled asthma despite INhaled corticosteroids (EINSTEIN): Protocol for a systematic review, network meta-analysis and cost effectiveness analysis using individual participant data (IPD)

Catrin Tudur Smith[1], Sarah Donegan[1], Sofia Cividini[1], Michelle Maden[2], Olive Fulton[*], Dyfrig Hughes[3], Steve Turner[4], Ian Sinha[5]

[1] *Department of Biostatistics, University of Liverpool*

[2] *Liverpool Reviews and Implementation Group (LRIG), University of Liverpool*

[3] *Centre for Health Economics & Medicines Evaluation, Bangor University*

[4] *University Court of the University of Aberdeen*

[5] *Alder Hey Children's Foundation NHS Trust*

[*] *Patients representative*

1. Abstract

Background

The British guideline on the management of asthma (1) recommends the stepping-up of treatment with pharmacological therapies for a child whose asthma remains uncontrolled despite regular treatment with inhaled corticosteroids (ICS). At present, there is no clear preferred option for initial step-up amongst the four treatment classes (inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), leukotriene receptor antagonists (LTRA), and Theophylline), and there is recognised heterogeneity of treatment response between individuals (2, 3). Existing evidence syntheses of aggregate trial-level data do not account for the impact of potential patient-level treatment effect modifiers due to limitations of reporting, lack of statistical power for testing treatment effect moderators, and the potential for misleading results due to aggregation bias (4). A robust, high-quality systematic review and Network Meta-analysis (NMA) based on re-analysing the individual participant data (IPD) from each included trial is urgently needed to overcome these limitations and provide an unbiased, reliable summary of the totality of evidence to support decision making.

Methods

This is a protocol for a systematic review and IPD-NMA of randomised controlled trials (RCTs), plus a Markov-based economic model. Inclusion criteria are clinical trials randomising children (aged < 18) with poor asthma control despite therapy with ICS, to at least one of the following pharmacological treatments: Inhaled Corticosteroids (ICS) alone or with add-on actives (Beclometasone dipropionate;

Ciclesonide; Fluticasone propionate and Fluticasone furoate; Budesonide; Mometasone); Long-acting β_2-agonists (LABA) (Formoterol; Salmeterol; Vilanterol); Leukotriene receptor antagonists (LTRA) (Zafirlukast; Montelukast); Theophylline. The primary outcomes are (i) Exacerbations and (ii) Asthma control. A Bayesian hierarchical meta-analysis model will be used to synthesise the available data based on direct evidence, and an NMA will be performed for each outcome. The probability that each treatment is the best, or worst, for a given outcome will be calculated. Potential patient-level characteristics that may modify treatment effects will be investigated. We will assess the cost-effectiveness of treatments by developing an economic model to estimate the incremental cost per quality-adjusted life-year gained.

Discussion

Results from the EINSTEIN collaborative IPD-NMA will provide clinicians, policy makers, and patients with up to date information, based on the totality of the evidence, about therapies for a child whose asthma remains uncontrolled despite regular treatment with ICS. Results are expected to be published in 2021.

Systematic review registration

PROSPERO (CRD42019127599)

2. Plain language summary

In the UK, over a million children have asthma, which causes symptoms of cough, noisy breathing, and shortness of breath, which can get suddenly worse during an asthma attack. Symptoms and asthma attacks can affect a child's overall wellbeing and quality of life, including their ability to attend school and play sports.

The first line of treatment is to give a child an inhaled steroid. If a child's asthma is still troublesome, various other medications can be used to help control the symptoms and prevent attacks. These will already have been tested in clinical trials (a type of research study) before being given to children by doctors.

The summary results from clinical trials should be published in medical journals and be used to compare the risks and benefits of treatments. Many clinical trials have been conducted in children with asthma, and these results are published in many medical journals. However, some clinical trials might not agree with other clinical trials, they may be of better quality than others, or they may not give very accurate results by themselves. It can, therefore, be very difficult for doctors, parents, and

children to make sense of this information and consider the best evidence to help them make important decisions. In the EINSTEIN study, we will bring together all of the available clinical trials and provide doctors and patients with a high-quality summary of all available information. We will use a process called a systematic review to identify all the relevant trials, assess their quality, and extract and summarise their results. We will then use a technique called network meta-analysis to join the results of different studies together to make it easier to understand and to find out which of the treatments is best.

In this project, we will also collect the individual participant data from each clinical trial rather than rely on the summary information that has been published in journal articles. This is very important as the summary results published in journals are known to be incomplete, sometimes inaccurate, and even presented in a biased or confusing way, which can mean that standard network meta-analyses using those data may be unreliable. Individual participant data will also help us to ask even more complex questions and look at whether features of a patient, such as age, gender, or asthma severity, could be used to tell how well they might respond to different treatments. Having this information would help inform choices about which medicine might be better for some patients and which should be avoided for others. This question can only be answered using the individual participant data.

Throughout this project, we will work with asthmatic children and their parents to ensure that we are asking relevant questions in the right way, and to help us learn how we can make our findings accessible and understandable. For example, we would ask them to help us prepare a podcast or leaflet that could be shared on asthma websites, and in clinics. We will share our findings at important international meetings, and in medical journals, and we want to make sure that this process reflects issues that are important to children and families. The EINSTEIN study will help doctors, parents, and children have the very best information available to decide which medicine is most likely to be the best for them at that particular time.

3. Background and rationale

Asthma remains a common medical condition affecting approximately 1 million children in the UK (5). Asthma causes symptoms of cough, wheeze, and breathlessness with acute asthma exacerbations occurring when children are exposed to various common triggers. The UK has among the highest prevalence rates of asthma symptoms in children worldwide with one child admitted to hospital every 20 minutes because of an asthma attack (5).

The aim of asthma management is to control the disease with complete control defined as (a) no daytime symptoms, (b) no night-time awakening due to asthma, (c) no need for rescue medication, (d) no asthma attacks, (e) no exacerbations, (f) no limitations on activity including exercise, (g) normal lung function (in practical terms, FEV1 and/or PEF >80% predicted or best), (h) minimal side effects from medication (1). The British Guideline on the management of asthma recommends that, following a diagnosis of asthma in a child, a stepwise approach to treatment should be taken. A short-acting β2 agonist (SABA) should be prescribed as needed, followed by regular use of an inhaled corticosteroid (ICS) at a low dose to improve symptom control as required. Treatment with a low dose inhaled corticosteroids (ICS) fails to control asthma symptoms in around 10-15% of children (6), in which case the guideline suggests ensuring adherence by giving appropriate information about the disease to children and their families, optimising inhaler technique, and treating co-morbidities such as rhinitis. Once these measures have been established, and if asthma remains uncontrolled, the guideline recommends a series of further steps, increasing treatment by including additional add-on preventer therapies of long-acting beta-agonists (LABA), leukotriene receptor antagonists (LTRA), increasing the dose of ICS, or adding SR Theophylline (1). Choosing the best step-up treatment is crucial to prevent exacerbations and avoid poor asthma control, which is associated with poor quality of life, increased risk of exacerbations, and hospital admissions, a negative impact on family life, reduced school attendance, and significant implications for NHS resources (7-12).

In a recent Cochrane review comparing LABA with ICS, evidence from 33 trials of 6381 children demonstrated that LABA added to ICS was not associated with a significant reduction in the rate of exacerbations requiring systemic steroids, but it was superior for improving lung function compared with the same or higher doses of ICS (13). No differences in adverse effects were apparent, with the exception of greater growth with the use of ICS and LABA compared with a higher ICS dose. The trend towards increased risk of hospital admission with LABA, irrespective of the dose of ICS, is a matter of concern that requires further monitoring (13). In a separate Cochrane review published in 2013, Chauhan et al. (14) found that the addition of LTRA to ICS is not associated with a statistically significant reduction in the need for rescue oral corticosteroids or hospital admission compared to the same or an increased dose of ICS in children and adolescents with mild to moderate asthma. The authors caution that the paucity of paediatric trials (evidence based only on 4 trials of 559 children at the time), the absence of data on pre-schoolers, and the variability in the reporting of relevant clinical outcomes considerably limits firm conclusions (14) regarding this comparison.

There are a number of RCTs that have compared two alternative step-up options head-to-head, but only a few individual trials have compared more than two classes head-to-head. The BADGER trial (3)

randomly assigned 182 children (6 to 17 years of age) with uncontrolled asthma on ICS 100 µg of fluticasone, to receive each of three blinded step-up therapies in random order for 16 weeks: 250 µg of Fluticasone twice daily (ICS step-up), 100 µg of Fluticasone plus 50 µg of a long-acting beta-agonist twice daily (LABA step-up), or 100 µg of Fluticasone plus 5 or 10 mg of a leukotriene-receptor antagonist daily (LTRA step-up). They found that nearly all the children had a differential response to each step-up therapy, but, on average, LABA step-up was significantly more likely to provide the 'best' response than either ICS or LTRA step-up. However, many children had a 'best' response to ICS or LTRA step-up therapy suggesting that for some patients these treatments are preferred. Of note is their definition of the response included a composite of three outcomes comprising exacerbation, asthma-control days, and the forced expiratory volume in 1 second, the latter of which is not essential to patients. In the NIHR HTA funded MASCOT trial (15), children aged 6-14 were randomised to either inhaled Fluticasone propionate 100µg twice daily plus placebo tablet once daily; inhaled Fluticasone propionate 100µg and Salmeterol 50µg twice daily (combination inhaler) plus placebo tablet once daily; or inhaled Fluticasone propionate 100µg twice daily plus Montelukast 5-mg tablet once daily. The MASCOT trial failed to recruit adequate numbers of patients due to significant challenges with the preparation, packaging, and supply of drugs delaying the start of the trial, followed by problems accessing patients from primary care and changes in prescribing habits throughout the trial. These challenges limit the potential for future similar trials to succeed, and recommendations have been made for the use of alternative study designs (15, 16) to compare alternative step-up treatments.

With over 10 potential treatments available, there will never be a single trial that compares all possible available treatments directly head-to-head, yet the fundamental question of interest to clinicians and patients is "Which of these treatments is best?". A network meta-analysis (NMA) is a technique that can be used to synthesise all the evidence and compare and rank all treatments on the basis of RCT results, even if treatments have not been directly compared with each other in a previous trial. Two NMAs, analysing published trial-level aggregate data for children with uncontrolled asthma, have already been conducted (17, 18), but the evidence from these analyses is severely limited. Published in 2012, Van der Mark (18) included 23 trials of 4129 patients, but due to huge variation in, and incomplete reporting of, outcome measurements across RCTs, a formal NMA and assessment of relative efficacies of treatments were not possible. A later publication in 2015 by Zhao et al. (17) succeeded in conducting a formal NMA of 35 trials of 12,010 children suggesting that combined ICS and LABA treatments were most effective in preventing exacerbations, and that medium- or high-dose ICS, combined ICS and LTRAs, and low-dose ICS treatments seem to be equally effective. However, there are several important limitations with their NMA, most notably that 70 relevant RCTs had been excluded because data about 'exacerbations' or 'symptom-free days' were not provided in trial

publications. Outcome reporting bias (19) is, therefore, a serious threat to the validity of their results if excluded studies had selectively reported results based on the statistical significance of their findings. Furthermore, the lack of complete overlap of studies compared with previous Cochrane reviews and the previous NMA by Van der Mark (18) (only 7 RCTs were in common across the two NMAs), the lack of analyses focussing on outcomes of importance and relevance to patients, and the lack of analyses comparing different drugs, doses and type of inhalation device within ICS, LABA and LTRA classes, makes the interpretation and generalisability of results of this NMA difficult.

At present, there is no clear preferred option for initial step-up since RCTs have found that all can be effective for groups of children considered collectively, but there is recognised heterogeneity of treatment response between individuals (2, 3). The BADGER trial (3) demonstrated that higher scores on the Asthma Control Test (ACT) (i.e., better disease control) predicted a better response to LABA step-up, but that LABA and LTRA did not differ significantly in patients with ACT scores of 19 or lower (i.e., worse disease control). These latter represent the group of children that are the more likely candidates for step-up options in real life. The authors also found that white race predicted a better response to LABA step-up, whereas black patients were least likely to have a best response to LTRA step-up. These results support a proposition that response to initial step-up treatment can vary according to a patient's characteristics. Further in-depth, robustly conducted analyses are required to thoroughly explore whether there is potential scope for a more individualised approach to asthma management to inform and empower children and parents to share in the decision-making process about treatment choices.

4. Why this research is needed now

Asthma is the most common long-term medical condition in children, affecting an average of three children in every classroom in the UK (5). The UK has among the highest prevalence rates of asthma symptoms in children worldwide. One in 11 children in the UK are currently receiving treatment for asthma, and the NHS spends around £1 billion a year treating and caring for people with asthma (5).

Clinical guidelines have been informed by previous clinical trials and systematic reviews comparing alternative step-up treatments, but these are aimed at "the average" patient, they make recommendations about classes of treatment, and they fail to adequately distinguish the potential for differential treatment response among children. Potential pharmacological differences (e.g., ICS/LABA combinations) and uncertainty around the clinical significance of these limits the extent to which we can inform and empower children and parents to share in the decision-making process about treatment choices. There is good evidence that clinicians are doing their own thing, regardless of the

guidelines (6), and feedback from our consultation with parents suggests that more needs to be done. There is an urgent need for a novel approach to be taken to synthesise all of the evidence using robust, unbiased methods. Results from the EINSTEIN study will provide clinicians and patients with accessible, high quality, patient-relevant information to help make evidence-informed treatment choices. Earlier identification of the best step-up treatment for a particular child could have a significant impact on children's lives with wider benefits to society and the NHS.

5. Aims and objectives

The EINSTEIN study will identify and synthesise all evidence from randomised controlled trials to establish the clinical effectiveness of pharmacological treatments for children with uncontrolled asthma on ICS. We will identify modifiers of treatment effect to optimise targeted treatment delivery and maximise patients' informed choice of treatment. We will assess the cost-effectiveness of treatments by developing an economic model to estimate the incremental cost per quality-adjusted life-year gained.

Specific objectives are:

i. Undertake a systematic review to identify relevant randomised controlled trials of treatment for children with asthma uncontrolled with inhaled corticosteroids (ICS)
ii. Collect individual participant data (IPD) from all eligible trials
iii. Conduct a network meta-analysis of IPD to identify the most effective treatment
iv. Identify modifiers of treatment effect to establish which patients respond better to each treatment
v. Construct an economic model to estimate the incremental cost per quality-adjusted life-year gained of treatment options, from the perspective of the NHS and personal social services
vi. Identify where uncertainties remain to produce recommendations to inform priorities for future research
vii. Disseminate findings

6. Methods

This is a protocol for a systematic review and individual participant data (IPD) network meta-analysis (NMA) of randomised controlled trials, plus a Markov-based economic model. The protocol has been registered in PROSPERO (CRD42019127599).

6.1. Inclusion and exclusion criteria

Each study identified as potentially eligible for the systematic review will be assessed for eligibility according to a set of criteria defined as follows.

Target population

Children aged < 18 that, despite therapy with ICS, have poor asthma control as defined by the study authors. We will include studies of mixed age groups for which children and adults were eligible because we will contact authors for specific data on children aged < 18.

Health technologies being assessed

Clinical trials randomising children to at least one of the following pharmacological treatments at any dose with any inhaler device (pressurised metered dose inhaler, dry powder inhaler, combination inhaler) will be included:

Inhaled Corticosteroids (ICS) (alone or with add-on actives): Beclometasone dipropionate; Ciclesonide; Fluticasone propionate and Fluticasone furoate; Budesonide; Mometasone;
Long-acting β_2-agonists (LABA): Formoterol; Salmeterol; Vilanterol
Leukotriene receptor antagonists (LTRA): Zafirlukast; Montelukast
Theophylline

Outcomes

To reduce potential for outcome reporting bias, all trials that meet the inclusion criteria will be included irrespective of the outcomes that have been reported within a trial publication. Contacting authors and collecting IPD may enable us to analyse outcome data that have not been previously analysed or reported.

Study design

Parallel and cross-over randomised controlled trials, of any duration, using any level of blinding, comparing at least one of the health technologies of interest will be included. Observational studies or controlled trials without adequate evidence of randomisation will be excluded.

6.2. Search strategy

Working with an experienced information specialist, a comprehensive approach for identifying published and unpublished studies will be undertaken. The search strategy will build upon that designed for two previously published aggregate data network meta-analyses (17, 18) and Cochrane

reviews (13, 14, 20-22) (see Appendix 1; for example, MEDLINE search). The search strategies will run from 2014 onwards only. From inception to 2013, we will consider as exhaustive the searches already carried out for the meta-analyses and Cochrane reviews above mentioned (13, 14, 17, 18, 20-22), and we will retrieve all the corresponding studies.

MEDLINE, the Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, NICE Technology Appraisals, and the NIHR HTA series will be searched using relevant search terms. The reference lists of existing clinical guidelines (e.g., British Guideline (1), Global Initiative for Asthma (GINA) (20)) along with included studies and relevant reviews will be checked to ensure that all studies are identified. Unpublished studies will be located by searching across a range of clinical trial registries that are included within the WHO International Clinical Trials Registry Platform search portal (including Clinicaltrials.gov and ISRCTN) and conference abstracts (e.g., European Respiratory Society, American Thoracic Society). Internal trial registers for pharmaceutical companies that manufacture health technologies of interest (e.g., GSK, Astra Zeneca, Novartis, Merck) will also be searched. The search will focus on identifying English language articles and will ensure that RCTs that have included participants aged < 18 as a subset are also identified. Studies identified for screening of abstracts and full-text articles will be managed within Covidence, a systematic review management tool.

6.3. Study selection and bias assessment

All studies will be assessed for inclusion by two independent reviewers with disagreements resolved through discussion with a third reviewer. The inclusion of trials will not be determined by the outcomes reported within a trial publication to minimise the impact of selective outcome reporting. Instead, we will record whether the outcomes of interest have been reported, formally assess the potential for outcome reporting bias, and request the IPD for all outcomes relevant to the review irrespective of whether these have been reported in the trial publications.

The Cochrane Risk of Bias tool will be used by two independent reviewers to record risk of bias with regard to randomisation method, allocation concealment, blinding, incomplete outcome data, and selective reporting.

6.4. Outcomes

Review outcomes will include the outcomes identified as important to healthcare practitioners and patients during the development of a core outcome set for trials in children with asthma (21, 22):

Primary Outcomes

1. Exacerbations as defined by ERS/ATS (22)
2. Asthma control measured by a validated test (e.g., ACT, ACQ, other).

Secondary Outcomes

3. Symptoms/symptom score
4. Quality of Life
5. Mortality (although rare, this was an important outcome for parents)
6. Physiological outcomes, e.g., FEV_1, bronchial responsiveness
7. Adverse effects (including growth and withdrawals due to adverse effects)
8. Hospital admissions
9. Cost, resource use, and utility outcomes to inform the economic model

6.5. Data collection

The first author, or sponsor, of each included trial will be approached and asked to supply anonymised IPD, metadata, and relevant documentation (23) (protocol and blank case report forms) from the respective trial. Methods that we have used to request IPD in previous systematic reviews (e.g., references (24-28)) will be used for making these data requests.

The data requested from each trial will include at least:

- Baseline characteristics – Age; sex; ethnicity; eczema; height; weight; baseline severity; baseline Peak Expiratory Flow Rate (PEFR); Forced Expiratory Volume in one second (FEV1)
- Date of randomisation and dates of follow-up visits
- Treatment details including inhalation device and dose
- Adherence data if available
- Data for the review outcomes along with details of their definitions and measurement tools used – Symptoms; Exacerbations; Asthma control; Mortality; Quality of Life; Growth; Physiological outcomes: Peak Expiratory Flow Rate (PEFR) and Forced Expiratory Volume in one second (FEV1); hospital admissions
- Cost, resource use, and utility outcomes to inform the economic model.

The anonymised IPD will be stored on a secure password protected server at the University of Liverpool with access granted to the project statistical team only. No attempt will be made to re-identify participants within datasets, and the copying or transfer of data to local computers, or data storage devices will be strictly prohibited. A range of standard quality and consistency checks of the data will be conducted, cross-checking the re-analysed IPD against previously published results to highlight inconsistencies or possible errors. Any queries will be raised with the original trialists

wherever possible. Data will be cleaned and standardised to allow pooling and subsequent analyses of the data.

Aggregate data such as the treatment level mean and standard deviation quality of life score at follow-up, or number of exacerbation events, available in trial publications will also be extracted for each trial to allow subsequent sensitivity analyses to explore the impact of missing IPD.

6.6. Data analysis

A full statistical analysis plan will be developed. Results of the screening process, including reasons for study exclusion will be summarised using a PRISMA flow diagram. Information about trial design, setting, treatment, dose, participant inclusion criteria, risk of bias, and other relevant data will be summarised in tables. We recognise that IPD may not be available for every trial, and there is a potential for data availability bias. However, previous studies have demonstrated that IPD can still be valuable for NMA even if only available for a subset of trials (29, 30) and IPD will be supplemented by relevant aggregate data from trials without IPD.

For each separate outcome, an NMA diagram will be constructed to display the number of studies and patients for each treatment comparison within the network. A Bayesian hierarchical meta-analysis model will be used to synthesise the available IPD, supplemented with aggregate data if necessary, to estimate the relative treatment effect (odds ratio for categorical data and difference in means for continuous data) and credibility interval for each pair-wise comparison based on direct evidence. The homogeneity assumption will be assessed by comparing the Deviance Information Criterion (DIC) of fixed-effect and random-effect models and observing the between trial variance. The forest plots, chi-square test for heterogeneity, and I^2 statistic will be examined to assess the evidence of heterogeneity within each pair-wise meta-analysis based on direct evidence.

An NMA will be performed for each outcome within a Bayesian framework, using the WinBUGS software with Goodness-of-fit assessed by calculating the posterior mean residual deviance with DIC used as a basis for model comparison. Correlation between treatment effects from multi-arm trials will be appropriately accounted for. From the NMA, the relative treatment effect for every pair-wise comparison can be estimated regardless of whether they have been compared directly in an RCT, and also the probability that each treatment is the best, or worst, for a given outcome can be calculated. In random-effects NMA models, it is conventional to assume the between trial variance is the same for each comparison. We will check this assumption by fitting pair-wise models based on direct evidence and assessing whether the variance is similar for each comparison. If the assumption appears unrealistic, we will explore other variance structures for the NMA model.

Validity of an NMA depends on the assumption that there is no effect modification of the pair-wise intervention effects, or that the prevalence of effect modifiers is similar in the different studies. The plausibility of this key assumption (often referred to as transitivity, similarity, and consistency) will be examined by comparing the inclusion/exclusion criteria of trials to make a judgement about whether patients, trial protocols, doses, administration, etc. are similar in ways that might modify treatment effect. We will use model fit and selection statistics to informally assess whether inconsistency is evident along with a formal analysis using a "node-splitting" approach (31, 32).

Potential patient-level characteristics that may modify treatment effects will be explored using hierarchical models with treatment by covariate interaction effects based on direct evidence initially, and subsequently in an NMA of the IPD, and aggregate data where IPD is unavailable (29, 33-35). The effect of covariates will be separated within and between trials. The underlying consistency assumption of these models will also be explored. Patient-level characteristics of interest include age, gender, ethnicity, eczema status, asthmatic phenotype (eosinophilic/non-eosinophilic), baseline %PEFR, and asthma severity. A literature search will be conducted to identify any further potential characteristics to explore.

The probability that a treatment is best and the probability that a particular treatment would be most likely to be effective for a specific patient profile will be calculated and summarised.

We will fit an NMA model to compare compounds within each class and separate models to compare the four classes of treatments. Furthermore, complex hierarchical models that account for both classes and compounds with covariate interactions will be explored.

Sensitivity analyses will be undertaken to explore the impact of missing IPD on results and conclusions of the NMA. Further sensitivity analyses will be explored to assess the robustness of results to different priors in the Bayesian analyses.

Adherence data will be requested as part of individual participant datasets, and this will be described noting differences in adherence rates between intervention arms within and across trials. However, our experience in this area suggests that it is likely that adherence data will either not have been collected or will have been collected using a variety of methods making meaningful analyses difficult. If sufficient data are available sensitivity analyses that adjust for levels of adherence will be conducted to assess the robustness of results obtained from the primary analysis, which will be on an intention-to-treat (ITT) basis.

6.6.1. Health economic modelling

Evidence on the cost-effectiveness of alternative treatment options will be important to inform decisions in the context of drug formularies and clinical guidelines. An economic analysis will be conducted using standard methods (36) based on the most robust data available and reported according to the CHEERS statement (37). Cost-effectiveness will be estimated from the perspective of the NHS and Personal Social Services in line with NICE guidance (38) and based on an economic model that considers health outcomes, resource use, costs, and health utilities to estimate the incremental cost per quality-adjusted life-year (QALY) gained of each treatment. We are aware of existing economic evaluations that may be informative in developing the analysis. However, a review of previous economic evaluations of relevant treatments of paediatric asthma will be performed to identify alternative model structures and key model parameters. The model structure will be developed in consultation with clinical experts to ensure it reflects a reasonable simplification of the context of care in the NHS.

The parameters needed to populate the models will include outcomes estimated by the network meta-analysis of the IPD (e.g., efficacy and safety parameters) and other parameters (e.g., utilities, resource use, and the long term costs of care) that will require searching of evidence beyond the studies included in the NMA. These will be sourced from a purposive review of the literature, and by using specialist databases (e.g., NHS EED for resource use parameters and the ScHARR Health Utilities Database for utility parameters) where necessary. Unit cost data will be derived from standard national sources (e.g., NHS reference costs (39) and the British National Formulary (40)).

A Markov model with a monthly cycle length will likely be necessary for longer term extrapolation of costs and outcomes to allow for any differential impacts of treatments over time and for transition of patients among the 5 steps of treatment. The model will evaluate costs and outcomes over the lifetime of the patient cohorts: costs and benefits in future years will be discounted at an annual rate of 3.5% and varied between 0% and 6% in sensitivity analysis. Results from the model will be reported as incremental cost per QALY gained (ICERs) and compared with the NICE threshold range of £20,000 to £30,000 per QALY.

Uncertainties in all parameter inputs will be accounted for in the analysis by including parametric distributions for each point estimate. Expert opinion will be used in cases where the evidence is not sufficiently detailed. This will enable probabilistic sensitivity analyses to be performed based on sampling from distributions using Monte Carlo simulation. The NMA estimates relative effects jointly, and the full joint distribution of these effects will be used in the economic model in order to preserve correlation (41). Uncertainty in the optimal treatment will be represented by cost-effectiveness acceptability curves (CEACs) (42), which present the probability that each drug is the most cost-

effective at a given threshold of cost effectiveness. Where the IPD-NMA indicates that patient characteristics modify treatment effects, a stratified approach will be used to assess cost-effectiveness in particular patient sub-group(s). Standard techniques (e.g., extreme value scenarios) will be used to ensure the internal validity of the model.

We will conduct a value of information analysis to inform future research priorities, e.g., whether more short-term efficacy trials are needed, or more long-term follow up, or more data on the utilities or costs to reduce decision uncertainty (43). The expected value of perfect information (EVPI) and the expected value of perfect parameter information (EVPPI) will be calculated on both per-patient and population levels using the Sheffield Accelerated Value of Information (SAVI) approximation (44) to facilitate computation effort. The EVPI for a decision problem must exceed the cost of research to make additional investigation worthwhile. It places an upper value on conducting further research overall (EVPI) or a specific area of information (EVPPI). If relatively small values are obtained for EVPI and EVPPI then this may suggest that no further research is necessary or required to obtain more precise estimates for specific parameters.

7. Dissemination and project outputs

We propose to disseminate findings in a number of ways. The systematic review and IPD-NMA protocol will be prepared according to the preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA-P) guidelines (45) and will be submitted for publication in an open access journal. The final completed systematic review and IPD-NMA will be prepared according to the PRISMA-IPD and PRISMA-NMA guidelines (46, 47) and will be submitted for publication in an open access medical journal with a full account of the economic evaluation published in a further open access journal. A full detailed account of the project will be provided in the final HTA report published on the NIHR journals library.

The 'EINSTEIN collaborative group' will be established and a representative from each identified trial invited to participate in the collaborative group. All subsequent publications utilizing the IPD will include the 'EINSTEIN collaborative group' as a co-author with appropriate recognition given to the original trialists.

Dissemination of results to patients and the public is a key component of this project. A plain language summary will be developed in collaboration with co-applicant Olive Fulton and with children and parents who are part of a recently established patient advisory group at Alder Hey Children's Hospital.

The plain language summary will be translated into a podcast and disseminated via patient groups, through contact with Asthma UK and the British Lung Foundation.

We will disseminate findings via local, national, and international meetings and conferences (e.g., European respiratory Society) and will work in close collaboration with the Press Offices of our HEIs to prepare timely press releases and increase awareness of our findings to the general public. A summary of results will be disseminated to NICE and BTS/SIGN as they will be highly relevant to future clinical guideline updates.

8. Ethical considerations

In any secondary research project using IPD collected from previous studies, the main concerns are focused on the protection of participant's confidentiality and concerns of inappropriate secondary analyses. We have a number of strategies in place, which have been tried and tested in several previous projects, to mitigate risks:

(i) we will ask for clarification that the original consent obtained from patients would not prevent the sharing of IPD for the purpose of this research

(ii) all IPD will be required to be anonymised before transfer

(iii) all IPD will be transferred using a secure data transfer system

(iv) all IPD will be stored on a secure password protected server at the Clinical Trials Research Centre at the University of Liverpool

(v) access to the IPD will be restricted to the statistical team

(vi) wherever relevant, a data use agreement will be signed to demonstrate our commitment to the safe storage and analysis of IPD supplied by trialists

(vii) all analyses will be pre-specified in a peer reviewed protocol including full statistical analysis plan with all results published as planned in the protocol

(viii) any safety concerns that may be uncovered from our analyses will be disseminated to the appropriate regulatory agency and pharmaceutical company

The University of Liverpool committee on Research Ethics has confirmed that ethics review is not required.

9. Patient and public involvement

Continuing the strong tradition at Alder Hey Children's Hospital of involving children in research, the EINSTEIN protocol has been developed in consultation with children with asthma and their parents, and with NHS clinicians who routinely care for children with uncontrolled asthma in NHS settings.

Firstly, we have sought advice on our proposal, and the lay summary, from five families, including two children, who attend our asthma clinic at Alder Hey. Secondly, the outcomes chosen in our review have been selected from a core outcome set which were agreed as important by clinicians and patients (21). This earlier work was heavily influenced by patients and, in particular, highlighted the importance to parents of including mortality and long-term adverse effects as outcomes.

Finally, we have recently established an Alder Hey patient advisory group, comprising children with asthma and their parents, to advise us on research studies in addition to clinical and service issues. We discussed the proposal with our advisory group and asked them to comment specifically on the lay summary and choice of outcomes in the review. Active involvement will continue to be present throughout the project.

10. Research Timetable

The project start date is 01/03/2019 with expected end date 28/2/2021

11. Funding

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12. Department of Health disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health

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Appendix 1. Example MEDLINE (OVID) search

1 exp Asthma/
2 asthma.ti,ab.
3 1 or 2
4 exp Infant/
5 infant*.ti,ab.
6 infancy.ti,ab.
7 newborn*.ti,ab.
8 baby*.ti,ab.
9 babies.ti,ab.
10 neonat*.ti,ab.
11 preterm*.ti,ab.
12 prematur*.ti,ab.
13 postmatur*.ti,ab.
14 exp child/
15 child*.ti,ab.
16 schoolchild*.ti,ab.
17 "school age*".ti,ab.
18 preschool*.ti,ab.
19 kid.ti,ab.
20 kids.ti,ab.
21 toddler*.ti,ab.
22 exp Adolescent/
23 adoles*.ti,ab.
24 teen*.ti,ab.
25 boy*.ti,ab.
26 girl*.ti,ab.
27 exp Minors/
28 minor*.ti,ab.
29 exp Puberty/
30 pubert*.ti,ab.
31 pubescen*.ti,ab.
32 prepubescen*.ti,ab.
33 exp Pediatrics/
34 paediatric*.ti,ab.
35 pediatric*.ti,ab.
36 exp Schools/
37 "nursery school*".ti,ab.
38 kindergar*.ti,ab.
39 "primary school*".ti,ab.
40 "secondary school*".ti,ab.
41 "elementary school*".ti,ab.
42 "high school*".ti,ab.
43 highschool*.ti,ab.
44 or/4-43
45 "inhaled corticosteroid*".mp.
46 ICS.mp.
47 exp Beclomethasone/
48 beclomethasone.mp.
49 "beclomethasone dipropionate".mp.
50 becotide.mp.

51 clenil.mp.
52 ciclesonide.mp.
53 "clenil modulite".mp.
54 exp Fluticasone/
55 "fluticasone propionate".mp.
56 fluticasone.mp.
57 flixotide.mp.
58 exp Budesonide/
59 budesonide.mp.
60 Mometasone Furoate/
61 mometasone.mp.
62 exp Adrenergic beta-Agonists/
63 "long acting beta-2 agonist*".mp.
64 "long acting beta2 agonist*".mp.
65 LABA.mp.
66 exp Formoterol Fumarate/
67 formoterol.mp.
68 Oxis.mp.
69 "fluticasone furoate".mp.
70 exp Salmeterol Xinafoate/
71 salmeterol.mp.
72 serevent.mp.
73 vilanterol.mp.
74 exp Leukotriene Antagonists/
75 "leukotriene receptor antagonist*".mp.
76 LTRA.mp.
77 zafirlukast.mp.
78 montelukast.mp.
79 exp Theophylline/
80 theophylline.mp.
81 Tiotropium.mp.
82 spiriva.mp.
83 Symbicort.mp.
84 Seretide.mp.
85 flutiform.mp.
86 relvar.mp.
87 or/45-86
88 Clinical Trial.pt.
89 Randomized Controlled Trial.pt.
90 exp Random Allocation/
91 exp Single-Blind Method/
92 exp Double-Blind Method/
93 exp Cross-Over Studies/
94 exp Placebos/
95 RCT.ti,ab.
96 Random*.ti,ab.
97 "Single blind*".ti,ab.
98 "Double blind*".ti,ab.
99 "triple blind*".ti,ab.
100 placebo*.ti,ab.
101 or/88-100

102 3 and 44 and 87 and 101
103 limit 102 to ed=20140701-20190911
104 limit 103 to english language
105 (case reports or editorial or letter).pt.
106 104 not 105

14. Protocol changes

Protocol version	Changes made	Date
1.0	NA	
2.0	(i) Section added to acknowledge funding source. (ii) Section added to acknowledge. Department of Health disclaimer. (iii) Section added to outline project start and end date. (iv) Section 'protocol changes' added.	22/8/2019
3.0	(i) It was specified that ICS will be considered alone or with add-on actives. (ii) Indacaterol was deleted from LABA. (iii) Further effect-modifiers added. (iv) The literature search strategy was updated. (v) References were updated.	27/02/2020