BMJ Open

Comparative effectiveness of inhaled corticosteroid for pediatric asthma: protocol for a Bayesian network meta-analysis

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008501
Article Type:	Protocol
Date Submitted by the Author:	16-Apr-2015
Complete List of Authors:	Takeuchi, Masato; Kikkoman General Hospital, Pediatrics Kano, Hirotsugu; Teikyo University School of Medicine University Hospital-Mizonokuchi, Pediatrics Takahashi, Kenzo; Teikyo University School of Medicine University Hospital-Mizonokuchi, Graduate School of Public Health Iwata, Tsutomu ; Tokyo Kasei University, Education for Childcare, Faculty of Child Studies
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Immunology (including allergy), Paediatrics
Keywords:	Paediatric thoracic medicine < PAEDIATRICS, Asthma < THORACIC MEDICINE, Allergy < THORACIC MEDICINE

For peer review only

SCHOLARONE™
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

Comparative effectiveness of inhaled corticosteroid for pediatric asthma: protocol for a Bayesian network meta-analysis

Masato Takeuchi[1], Hirotsugu Kano[2], Kenzo Takahashi[3] and Tsutomu Iwata[4]

1: Department of Pediatrics, Kikkoman General Hospital, Chiba, Japan

2: Department of Pediatrics, Teikyo University School of Medicine University Hospital-Mizonokuchi, Kanagawa, Japan

3: Graduate School of Public Health, Teikyo University, Tokyo, Japan

4: Department of Education for Childcare, Faculty of Child Studies, Tokyo Kasei University, Saitama, Japan

Corresponding author: Dr. Masato Takeuchi

Department of Pediatrics, Kikkoman General Hospital,

100 Miyazaki, Noda, Chiba, 278-0005, Japan

Tel: +81-4-7123-5911; e-mail: masatotakeuchi@gmail.com

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

For peer review only

ABSTRACT

Introduction: Inhaled corticosteroid (ICS) is the mainstream maintenance therapy for pediatric asthma. Several forms of ICS are available, but the relative effectiveness among ICSs has not been well investigated in published randomized controlled trials. The paucity of direct comparisons among ICS may have resulted in insufficient estimation in former systematic reviews/meta-analyses. To supplement the information on comparative effectiveness of ICS for pediatric asthma, we plan to conduct a network meta-analysis (NMA) that will enable summary of direct and indirect evidence.

Methods and analysis: We will retrieve randomized controlled trials that examine the effectiveness of ICS for pediatric asthma from the Cochrane Central Register of Controlled Trials. After one author scans the title and abstract for eligible studies, two authors will independently review study data and assess the study quality. Studies of children with chronic asthma or recurrent wheezing episodes will be included if they use ICS for ≥4 weeks. We will not define the primary outcome in this study because no single outcome measure actually represents control of asthma. We will assess multiple asthma outcomes to determine a more complete understanding of asthma control by ICS,

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

including pulmonary function, rescue use of medications, and urgent health service use. Extracted data will be synthesized in the Bayesian framework using the random effects model.

Ethics and dissemination: The results will be disseminated through peer-reviewed publications and conference presentations.

Protocol Registration: UMIN000016724

Strengths and limitations of this study

- This study will be the first meta-analysis that examines comparative effectiveness of inhaled corticosteroids for pediatric asthma
- The result of this study will aid clinical decision making for practitioners and will be the basis of future cost effective analysis.
- The potential limitation of our study is that it only includes published trials, which may be affected by some bias (eg, publication bias)

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

INTRODUCTION

Morbidity of pediatric asthma is substantial worldwide. The prevalence of childhood asthma differs among countries(1), and up to 20–25% of children have prescriptions for anti-asthma medications in some industrialized countries(2, 3). Data from the USA represent an example of the asthma-related burden in children. These data show that, in 1 year, asthma causes exacerbations in 57% of pediatric patients, 12.8 million missed school days, 198,000 hospitalizations (the third cause of all childhood hospitalizations), and 185 deaths(1, 4).

Asthma is characterized by chronic inflammation of the airway(5) and thus, for control of airway inflammation, regular maintenance therapy is required in most patients(6, 7). Inhaled corticosteroid (ICS) is the mainstream of asthma treatment in adults and children. ICS use achieves asthma control and this therapy leads to fewer exacerbations, emergency department visits, and hospitalization(8). ICS also improves other outcome measures of asthma, such as pulmonary function(9) and quality of life (QOL) of patients(10).

There are several forms of ICSs for pediatric patients. Fluticasone propionate

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

(FP), hydrofluoroalkane-134a beclomethasone (HFA-BDP), budesonide (BUD), and ciclesonide (CIC) are commonly prescribed ICSs for pediatric asthma(11). The relative effectiveness of these agents is estimated by their potency in vitro(12). Based on in vitro observations, the effectiveness of different ICSs is often assumed to be similar (i.e., 1:1 ratio in equivalent dose) in vivo. However, ICSs have different properties(8); FP has a potent affinity for steroid receptors with a long half-life(13), HFA-BDP is composed of small particles and can be delivered to small airways(14), and BUD suspension is easy to use in children who are not cooperative with inhalation therapy(15). Because of differences in formulations and delivery systems, the effectiveness of ICS can differ clinically(16). A medical database study from the USA reported that asthma control might be better in patients with HFA-BDP than in those with FP(17). However, few studies have compared different types of ICS directly(18). One systematic review concluded that there was little evidence of comparative effectiveness of ciclesonide (CIC) with other ICSs among adult patients(19). This review was restricted to small, phase 2 studies of low power. The authors found only five randomized, controlled trials (RCTs) with a total of 84 patients(19).

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

One strategy to improve the statistical power of small studies is to conduct a meta-analysis(20). However, as mentioned above, studies comparing different classes of ICS are limited. The majority of clinical trials compared ICSs with other classes of drugs (e.g., antileukotrienes or ICS/long-acting beta-agonist [LABA] combination) or placebo. The paucity of trials of a direct comparison makes it difficult to perform a conventional meta-analysis (hereafter, we use the term "pairwise meta-analysis"). Recently, a novel meta-analytic technique called a network meta-analysis (NMA) was developed, and this enables results of trials to be combined in a direct and indirect manner(21-23).

In this context, we plan to conduct an NMA to address the following open question: Are there any differences in effectiveness among ICSs for pediatric asthma?

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

METHODS AND ANALYSIS

Goal of the study

We aimed to evaluate the comparative effectiveness of different ICSs for pediatric asthma. For this purpose, we will use the NMA approach to synthesize two types of clinical trials together: trials comparing different ICSs directly and trials comparing ICSs with other classes of intervention (e.g., antileukotrienes or placebo).

Agreement with PRISMA-P 2015

For developing this protocol, we referred to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement(24), a guide for standard reporting of systematic review protocols. However, our protocol does not always adhere to PRISMA-P items. For example, PRISMA-P specifically encourages registration of the protocol to PROSPERO(25) because this site was the only option at the timing of preparation of PRISMA-P (item 2). Instead of PROSPERO, we have registered this protocol at UMIN(26), which launched registration of systematic reviews on January 29, 2013 (available in English as well as Japanese). Additionally, although

For peer review only

PRISMA-P recommends deciding on the primary outcome (item 13), we did not specify a single primary outcome in the present study (discussed below). Overall, this protocol follows the PRISMA-P statement, but differs to a reasonable extent.

Inclusion criteria: participants, interventions, comparisons, and outcomes

Participants

Studies of children with chronic or persistent asthma will be included. We will accept the definitions for "children" as used by the investigators in the original studies. We will include studies exclusively comprising pediatric patients and those involving adult and pediatric patients if data of pediatric age groups are separately presented and can be extracted.

This meta-analysis will also include studies of "children with recurrent wheeze" or "preschool wheezer". Currently, the diagnosis of asthma in young children is challenging because there are no universally accepted diagnostic criteria(27). Only a subset of young children with recurrent wheezing episodes later develops physician-diagnosed asthma(28, 29). In addition, there is a wide range of differential

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

diagnosis in recurrent wheeze that mimics pediatric asthma, such as cystic fibrosis, congenital malformation of the airways, and foreign body aspiration(30). Therefore, children with recurrent wheeze may or may not have asthma. The likelihood of asthma in such patients depends on the presence/absence of risk factors (e.g., family history)(31). Despite these problematic issues, we have decided to enroll children with recurrent wheeze for the following three reasons. First, recurrent wheezing is a major risk factor of asthma; as shown in studies of the Asthma Predictive Index, the combination of wheezing episodes ≥three episodes/year and other criteria is strongly associated with the risk of asthma (up to 77% chance of active asthma)(29). Second, in addition to symptoms and risk factors, the therapeutic response is often important for diagnosis of pediatric asthma(31,32) and empirical evidence indicates that children with recurrent wheeze may benefit from regular ICS use(30). Finally, previous systematic reviews/meta-analyses did not often distinguish children with asthma from those with recurrent wheeze(33). Because of these reasons, we consider that children with asthma and those with recurrent wheeze share similar (although not identical) clinical characteristics and responses to ICS therapy. In trials of children with recurrent wheeze,

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

we will carefully review (1) whether confirmation of wheezing episode relies on a physician's diagnosis or a patient's self-report (2), whether the risk factors of asthma (e.g., atopic status or family history) are described, and (3) whether differential diagnoses of wheeze are investigated. If these issues are insufficiently examined or documented, the authors will discuss whether such reports will be eligible for inclusion into the meta-analysis.

Interventions

We will include RCTs to examine the effectiveness of ICS in asthmatic children for ≥4 weeks. We will only include studies using ICS without co-interventions because the effectiveness of ICS is difficult to assess separately in trials with co-intervention (e.g., ICS/LABA combination therapy). We will limit studies evaluating the effectiveness of ICS in current use (i.e., studies of ICSs that are no longer used, such as HFA-chlorofluorocarbon, will be excluded)

Comparisons

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

This study will include clinical trials comparing one ICS with other active or inactive intervention(s), such as other types of ICSs, other classes of drugs (e.g., antileukotrienes) or placebo. The comparator should also be a single intervention because of the reason mentioned above.

Outcomes

In meta-analyses, researchers often declare the primary endpoint of the study(34, 35). However, this practice is difficult in asthma studies(36). There are several domains in asthma control, such as a pulmonary function test or symptoms (e.g., exacerbation), and according to expert opinion, no single primary endpoint is recommended for assessment of responses to asthma(37). Therefore, our planned study will not define a single primary endpoint, and instead, will examine different endpoints to determine a more complete understanding of asthma control by ICS(37).

Study outcomes should be clinically relevant, and ideally, they should be patient-centered(38). Additionally, outcomes should be used in a sufficiently large number of trials to be pooled in the analysis. Summarizing a large sample size would

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

lead to more precise and confident estimation, and in NMA, combining small sample size studies could result in biased estimates(39). From these perspectives, we will not include studies that exclusively examined biomarkers, QOL, or severity scores for the following reasons. First, how these outcomes correlate with the clinical benefit has yet to be established, and the magnitude of benefit of these outcomes is difficult to interpret for patients and even for health-care professionals(37). Second, a previous systematic review identified a few studies that examined these outcomes in pediatric patients(40). Finally, for QOL and severity scores, different formulations are available and they are not interchangeable with each other(41).

Exclusion criteria

We will exclude the following literature: abstracts only (e.g., conference paper), studies that are not on asthma (e.g., viral bronchiolitis), studies examining the dose–response relationship of ICS (because of technical difficulties in incorporating data into the meta-analysis), safety assessment studies of ICS, and short-term or intermittent use of ICS.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

Literature search

The primary literature search will rely on the Cochrane Central Register of Controlled Trials (CENTRAL), which is a bibliographic database of RCTs retrieved from MEDLINE, EMBASE, and records through manual searching We will use medical subject headings and text words related to “child”, “asthma”, and “ICS” for the literature search(40). To ensure literature saturation, we will scan the reference lists of included studies or relevant reviews that are identified through the search

Selection of studies and extraction of data

One of the authors (MT) will scan the title and abstract of all the literature that is retrieved by the initial search and select eligible articles for review of the full text. The other two authors (HK and KT) will independently review full-text articles to assess eligibility and select citations to be meta-analyzed. They will also extract data independently using a prestandardized data abstraction form. Any disagreements will be resolved by discussion among all of the authors.

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Quality assessment

We will assess the quality and risk of bias of eligible studies, including the method of randomization, treatment allocation concealment, blinding the outcome assessor, and dropouts. The checklist prepared for RCTs will be used(42, 43). We will also rely on the Grading of Recommendations Assessment, Development and Evaluation approach for quality assessment in cumulative estimates.

Statistical methods

Fig. 1a illustrates the scheme of the proposed pairwise meta-analysis. A pairwise meta-analysis can compare head-to-head trials (Fig. 1a, A vs B and A vs C), but cannot compare indirect arms (Fig. 1a, B vs C). In contrast, NMA can compare indirect arms (Fig. 1a, B vs C). Based on a "consistency assumption", the indirect effectB-C represents the difference between effectA-B and effectA-C (in this case, intervention A is referred to as a common comparator)(23, 44). Moreover, when there are head-to-head trials between B and C (Fig. 1b), NMA can combine the direct effectB-C and indirect

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

effectB-C (i.e., effectA-B – effectA-C)(45). In this way, NMA combines all available evidence of direct and indirect comparisons. There is an additional strength in NMA. A pairwise meta-analysis can compare only two interventions at a time(23). In a situation in Fig. 1b, comparison of "A vs B vs C" is not feasible, even when direct comparisons exist. In contrast, NMA can compare ≥three interventions and determine which treatment works best. Further, NMA can compare more complex network loops (Fig. 2). Fig. 2 shows that comparative effectiveness among the ICSs' X, Y and Z can be estimated by combining direct evidence (effectB-C) and indirect effects using drug A and placebo as a common comparator. Based on these strengths in NMA, we will evaluate comparative effectiveness of ICS by pooling the results from head-to-head trials of ICS and from indirect comparisons among different ICSs using placebo or other classes of medications (e.g., antileukotriene drugs) as a common comparator.

Statistical analyses will be conducted in a Bayesian hierarchical framework using a random effects model(46). We will use the gemtc package in R statistical software (47, 48). This package employs a method developed by Lu and Ades(22). This package also allows us to check for homogeneity and consistency, which are important

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

assumptions in NMA that combined studies should be similar in clinical and statistical context (often referred to as transitivity assumption(23)). If large heterogeneity is detected, subgroup analyses will be conducted. As an example of this situation, when the dosage of ICS varies considerably among studies, we will stratify studies of "low", "medium" and "high" dose(18), and combine the results within each strata. The statistical analyses will be performed by one author (MT) on the basis of previous expertise(49).

Role of the funding source

This study is funded by the Japanese Society of Pediatric Allergy and Clinical Immunology. There is no role of the funding source in the study design, data collection and analysis, interpretation of results, or manuscript preparation and submission.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

DISCUSSION

This protocol paper presents the hypothesis, rationale, and methodology of our planned study.

The relative potency of different ICSs has been the subject of considerable dispute and debate(12). Comparative dosing charts among ICSs have been proposed, (e.g., by an expert panel) (50) and they rely on comparative efficacy trials in vitro. Few studies have assessed relative therapeutic indices among ICSs(18, 51) and whether there are clinical differences among ICSs remains uncertain. To challenge this open question, we plan to conduct NMA, a newly developed meta-analytic technique.

NMA (also known as a multiple treatment comparison meta-analysis or mixed treatment meta-analysis) has gained popularity in recent years (23, 44), in light of comparative effectiveness research (CER). By definition, CER refers to studies that compare the benefits and harms of different interventions(52). The objectives of CER include helping physicians use existing treatments and treatment strategies more effectively(53). CER also aims to determine which interventions and strategies are most effective, safest, or least costly when multiple options are available(53). CER is an emerging research

For peer review only

area that is crucial for helping clinical decision making. However, within the current framework of medicine, limited data are available among different interventions. Comparative efficacy data are often lacking at preapproval and postapproval of medications (53 - 55). To bridge the gap between the needs and the lack of CER studies, new clinical trials or systematic reviews/meta-analyses, specifically NMA, are the priorities for future research(56). Our planned study to determine the comparative effectiveness of ICS for pediatric asthma is in line with the current effort for CER.

Relevance and credibility are two essential components in NMA(57). The expected results of our study will be relevant in that they will be applicable to clinical settings of interest to asthmatic patients or health-care providers. We hope that the results in this NMA study will be credible, providing valid answers to the research question of "Are there any differences in effectiveness among ICSs for pediatric asthma?"

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

ETHICS AND DISSEMINATION

No ethical approval is required because this study will include published clinical trials with no personal data of patients.

The results of this study will be submitted to a peer-reviewed journal for publication and will also be presented at future conferences.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

Contributors

All authors made substantial contributions to the conception and design of the study. MT prepared the first draft of the article. HK, KT, and TI critically revised the manuscript for important intellectual content. All of the authors provided final approval of the version to be published.

Funding

This study is funded by the Japanese Society of Pediatric Allergy and Clinical Immunology.

Competing interests

None.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

REFERENCES

1. Guilbert T, Moss HM, Lemanske RF Jr . Approach to Infants and Children with Asthma. In; Adkinson NF Jr, Bochner BS, Busse WW Holgate SH, Lemanske RF Jr, Simons FE, eds. Middleton's Allergy: Principles and Practice. Philadelphia; Saunders 2009: 1319-44

2. Bianchi M, Clavenna A, Labate L, Bortolotti A, Fortino I, Merlino L, et al. Anti-asthmatic drug prescriptions to an Italian paedriatic population. *Pediatr Allergy Immunol* 2009;20:585-91.

3. Bianchi M, Clavenna A, Bonati M. Inter-country variations in anti-asthmatic drug prescriptions for children. Systematic review of studies published during the 2000-2009 period. *Eur J Clin Pharmacol*. 2010;66:929-36.

4. Centers for Disease Control and Prevention. CDC vital signs: Asthma in the US 2011. Available from: http://www.cdc.gov/vitalsigns/pdf/2011-05-vitalsigns.pdf. [accessed 16 Mar 2015]

5. Hanania NA. Targeting airway inflammation in asthma: current and future therapies. *Chest*. 2008;133:989-98.

For peer review only

6. Rank MA, Hagan JB, Park MA, Podjasek JC, Samant SA, Volcheck GW, et al. The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: a systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol*. 2013;131:724-9.

7. Morton RW, Everard ML, Elphick HE. Adherence in childhood asthma: the elephant in the room. *Arch Dis Child*. 2014;99:949-53.

8. Cerasoli F, Jr. Developing the ideal inhaled corticosteroid. *Chest*. 2006;130(1 Suppl):54S-64S.

9. Raissy HH, Kelly HW, Harkins M, Szefler SJ. Inhaled corticosteroids in lung diseases. *Am J Respir Crit Care Med*. 2013;187:798-803.

10. Murphy KR, Fitzpatrick S, Cruz-Rivera M, Miller CJ, Parasuraman B. Effects of budesonide inhalation suspension compared with cromolyn sodium nebulizer solution on health status and caregiver quality of life in childhood asthma. *Pediatrics*. 2003;112:e212-9.

11. The Thoracic Society of Australia and New Zealand. The Role of Corticosteroids in the Management of Childhood Asthma. 2010. Available from:

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

http://www.thoracic.org.au/imagesDB/wysiwyg/Steroidsinasthma_2010.pdf. [accessed 16 Mar 2015]

12. Barnes NC. The properties of inhaled corticosteroids: similarities and differences. *Prim Care Respir J*. 2007;16:149-54.

13. Derendorf H, Hochhaus G, Meibohm B, Mollmann H, Barth J. Pharmacokinetics and pharmacodynamics of inhaled corticosteroids. *J Allergy Clin Immunol*. 1998;101:S440-6.

14. Vanden Burgt JA, Busse WW, Martin RJ, Szefler SJ, Donnell D. Efficacy and safety overview of a new inhaled corticosteroid, QVAR (hydrofluoroalkane-beclomethasone extrafine inhalation aerosol), in asthma. *J Allergy Clin Immunol*. 2000;106:1209-26.

15. Szefler SJ, Eigen H. Budesonide inhalation suspension: a nebulized corticosteroid for persistent asthma. *J Allergy Clin Immunol*. 2002;109:730-42.

16. Baptist AP, Reddy RC. Inhaled corticosteroids for asthma: are they all the same? *J Clin Pharm Ther*. 2009;34:1-12.

17. Colice G, Martin RJ, Israel E, Roche N, Barnes N, Burden A, et al. Asthma outcomes and costs of therapy with extrafine beclomethasone and fluticasone. *J Allergy*

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

Clin Immunol. 2013;132:45-54.

18. Kelly HW. Comparison of inhaled corticosteroids: an update. *Ann Pharmacother*. 2009;43:519-27.

19. Dyer MJ, Halpin DM, Stein K. Inhaled ciclesonide versus inhaled budesonide or inhaled beclomethasone or inhaled fluticasone for chronic asthma in adults: a systematic review. *BMC Fam Pract*. 2006;7:34.

20. Thacker SB. Meta-analysis. A quantitative approach to research integration. *JAMA*. 1988;259:1685-9.

21. Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med*. 2002;21:2313-24.

22. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23:3105-24.

23. Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med*. 2013;159:130-7.

24. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

statement. *Syst Rev*. 2015;4:1.

25. University of York, Centre for Reviews and Dissemination. Available from: http://www.crd.york.ac.uk/PROSPERO/. [accessed 16 Mar 2015]

26. University hospital Medical Information Network (UMIN) Center. Available from: http://www.umin.ac.jp/. [in Japanese] [accessed 16 Mar 2015]

27. Cave AJ, Atkinson LL. Asthma in preschool children: a review of the diagnostic challenges. *J Am Board Fam Med*. 2014;27:538-48.

28. Pescatore AM, Dogaru CM, Duembgen L, Silverman M, Gaillard EA, Spycher BD, et al. A simple asthma prediction tool for preschool children with wheeze or cough. *J Allergy Clin Immunol*. 2014;133:111-8. e13.

29. Castro-Rodriguez JA. The Asthma Predictive Index: a very useful tool for predicting asthma in young children. *J Allergy Clin Immunol*. 2010;126:212-6.

30. Ducharme FM, Tse SM, Chauhan B. Diagnosis, management, and prognosis of preschool wheeze. *Lancet*. 2014;383:1593-6

31. Bacharier LB, Guilbert TW. Diagnosis and management of early asthma in preschool-aged children. J *Allergy Clin Immunol*. 2012;130:287-96;

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

32. Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Gotz M, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy*. 2008;63:5-34.

33. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics*. 2009;123:e519-25.

34. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;349:g7647.

35. Rangwalla SC, Waljee AK, Higgins PD. Voting With their Feet (VWF) endpoint: a meta-analysis of an alternative endpoint in clinical trials, using 5-ASA induction studies in ulcerative colitis. *Inflamm Bowel Dis*. 2009;15:422-8.

36. Busse WW, Morgan WJ, Taggart V, Togias A. Asthma outcomes workshop: overview. *J Allergy Clin Immunol*. 2012;129(Suppl):S1-8.

37. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009;180:59-99.

38. Frank L, Basch E, Selby JV. The PCORI perspective on patient-centered outcomes research. *JAMA*. 2014;312:1513-4.

39. Dawn Odom CC, Beth Sherrill, Jianmin Wang, Bintu Sherif. Practical Issues When Conducting Network Meta-Analyses With a Limited Number of Studies [abstract]. ISPOR 19th Annual International Meeting; Montreal, QC, Canada2014.

40. Sinha IP, Williamson PR, Smyth RL. Outcomes in clinical trials of inhaled corticosteroids for children with asthma are narrowly focussed on short term disease activity. *PLoS One*. 2009;4:e6276.

41. Parulekar AD, Alobaidy A, Hanania NA. Asthma outcomes revisited. *Curr Opin Pulm Med*. 2013;19:6-12.

42. The Cochrane Collaboration's tool for assessing risk of bias. Available from: http://ohg.cochrane.org/sites/ohg.cochrane.org/files/uploads/Risk%20of%20bias%20assessment%20tool.pdf. [accessed 16 Mar 2015]

43. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.

44. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *BMJ*. 2013;346:f2914.

45. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ*. 2005;331:897-900.

46. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making*. 2013;33:607-17.

47. GeMTC R package. http://drugis.org/software/r-packages/gemtc [accessed 16 Mar 2015]

48. Neupane B, Richer D, Bonner AJ, Kibret T, Beyene J. Network meta-analysis using R: a review of currently available automated packages. *PLoS One*. 2014;9:e115065.

49. Takeuchi M. Bayesian network meta-analysis suggests a similar effectiveness between a monovalent and a pentavalent rotavirus vaccine: a preliminary report of re-analyses of data from a Cochrane Database Systematic Review. *Hum Vaccin*

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

Immunother. 2014;10:1421-4.

50. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(Suppl):S94-138.

51. Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, et al. Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in children under the age of 12 years. *Health Technol Assess*. 2008;12:1-174.

52. Sox HC. Defining comparative effectiveness research: the importance of getting it right. *Med Care*. 2010;48(Suppl):S7-8.

53. Hochman M, McCormick D. Characteristics of published comparative effectiveness studies of medications. *JAMA*. 2010;303:951-8.

54. Goldberg NH, Schneeweiss S, Kowal MK, Gagne JJ. Availability of comparative efficacy data at the time of drug approval in the United States. *JAMA*. 2011;305:1786-9.

55. Thomas RH, Freeman MK, Hughes PJ. Preapproval and postapproval availability of published comparative efficacy research on biological agents. *Am J Health Syst Pharm*.

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

2013;70:1250-5.

56. Li T, Vedula SS, Scherer R, Dickersin K. What comparative effectiveness research is needed? A framework for using guidelines and systematic reviews to identify evidence gaps and research priorities. *Ann Intern Med*. 2012;156:367-77.

57. Jansen JP, Trikalinos T, Cappelleri JC, Daw J, Andes S, Eldessouki R, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health*. 2014;17:157-73.

Figure legends

For peer review only

BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

Figure 1a: Scheme for pairwise meta-analysis. In this example, a comparison of "B vs. C" is impractical.

Figure 1b: Scheme for pairwise and network (indirect) meta-analysis. An indirect comparison of "B vs. C" can be estimated from knowledge of "A vs. B" and "A vs. C" trials.

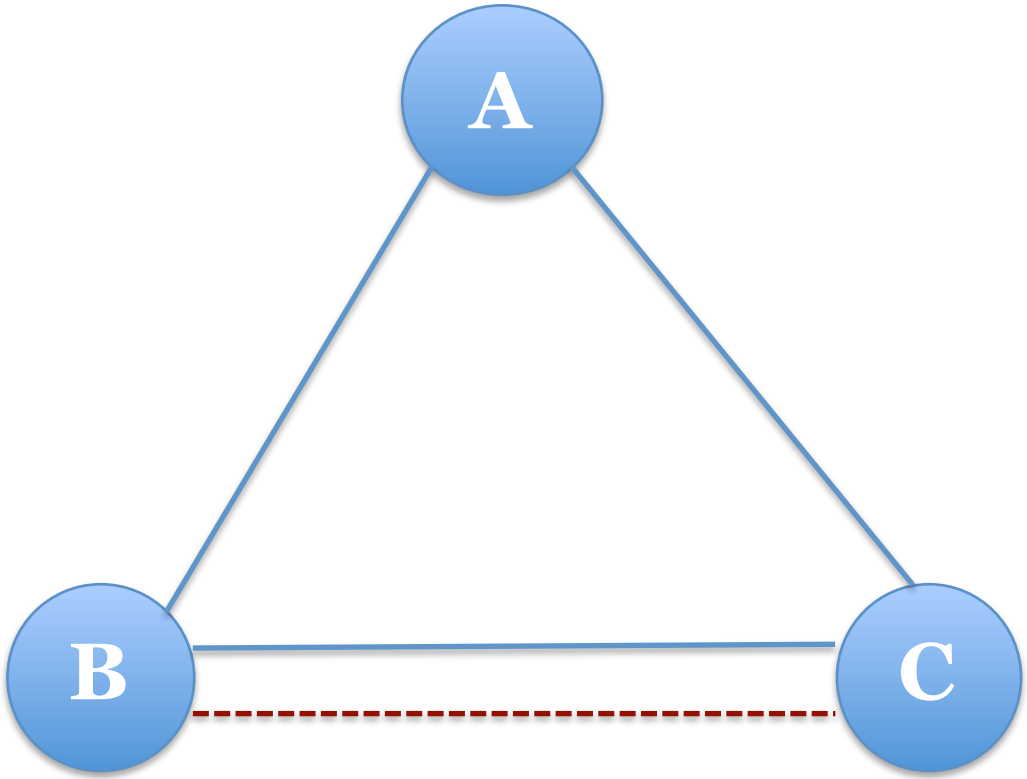
Figure 2: Scheme for a complex network in network meta-analysis.

NMA: network meta-analysis.

For peer review only

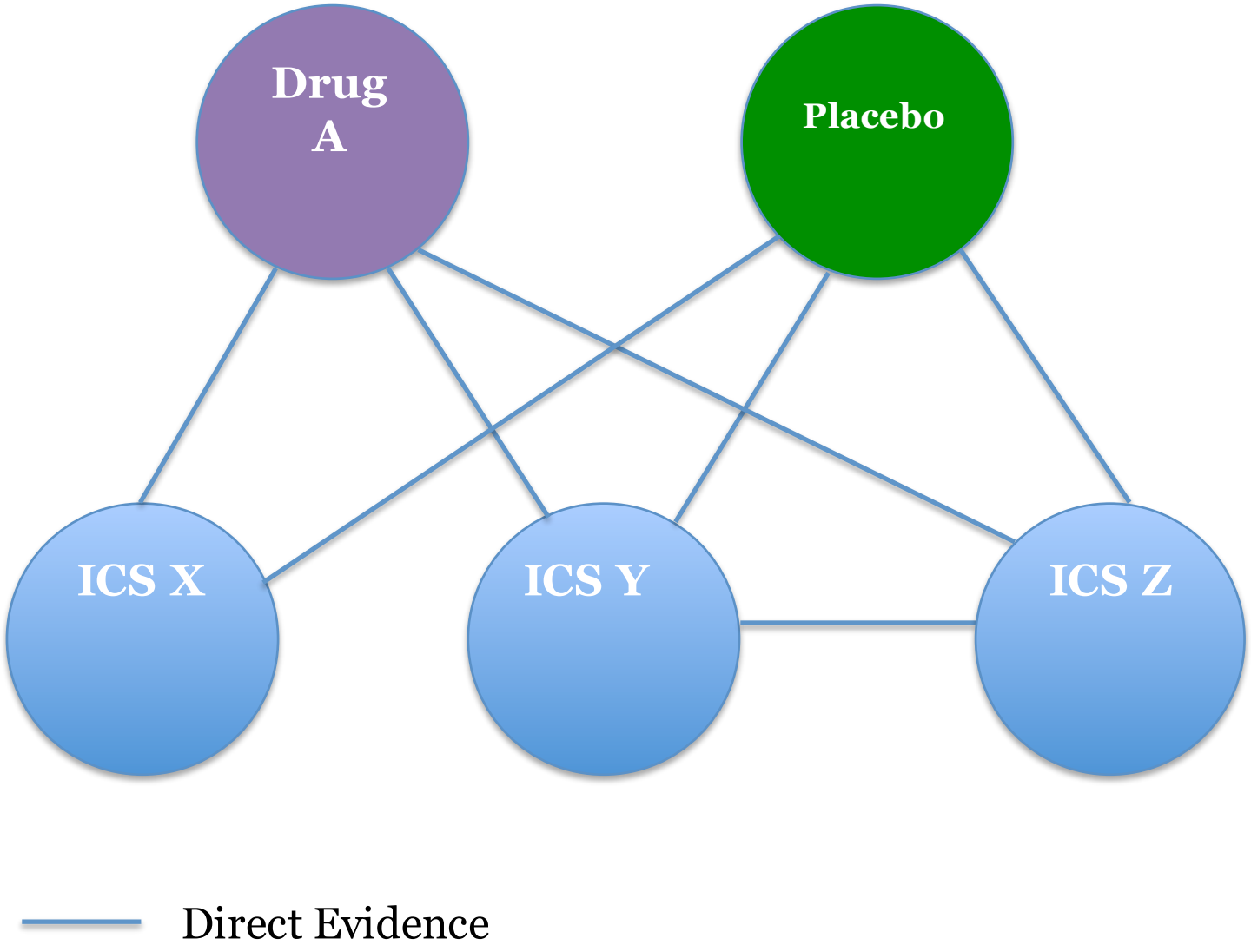
BMJ Open: first published as 10.1136/bmjopen-2015-008501 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

1 on 22 October 2015. Downloaded from http://bmjopen.bmj.com/ on April 18, 2024 by guest. Protected by copyright.



Direct Evidence
Indirect Evidence
} Combine both Evidence in NMA (if any)

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml


Drug A
Placebo
ICS X
ICS Y
ICS Z
Direct Evidence

BMJ Open

Comparative effectiveness of inhaled corticosteroid for pediatric asthma: protocol for a systematic review and Bayesian network meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-008501.R1
Article Type:	Protocol
Date Submitted by the Author:	09-Sep-2015
Complete List of Authors:	Takeuchi, Masato; Kikkoman General Hospital, Pediatrics Kano, Hirotsugu; Teikyo University School of Medicine University Hospital-Mizonokuchi, Pediatrics Takahashi, Kenzo; Teikyo University School of Medicine University Hospital-Mizonokuchi, Graduate School of Public Health Iwata, Tsutomu ; Tokyo Kasei University, Education for Childcare, Faculty of Child Studies
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Immunology (including allergy), Paediatrics
Keywords:	Paediatric thoracic medicine < PAEDIATRICS, Asthma < THORACIC MEDICINE, Allergy < THORACIC MEDICINE

SCHOLARONE™
Manuscripts

For peer review only

Comparative effectiveness of inhaled corticosteroid for pediatric asthma: protocol for a systematic review and Bayesian network meta-analysis

Masato Takeuchi[1], Hirotsugu Kano[2], Kenzo Takahashi[3] and Tsutomu Iwata[4]

1: Department of Pediatrics, Kikkoman General Hospital, Chiba, Japan

2: Department of Pediatrics, Teikyo University School of Medicine University Hospital-Mizonokuchi, Kanagawa, Japan

3: Graduate School of Public Health, Teikyo University, Tokyo, Japan

4: Department of Education for Childcare, Faculty of Child Studies, Tokyo Kasei University, Saitama, Japan

Corresponding author: Dr. Masato Takeuchi

Department of Pediatrics, Kikkoman General Hospital,

100 Miyazaki, Noda, Chiba 278-0005, Japan

Tel: +81-4-7123-5911; e-mail: masatotakeuchi@gmail.com

For peer review only

For peer review only

ABSTRACT

Introduction: Inhaled corticosteroid (ICS) is the mainstream maintenance therapy for pediatric asthma. Several forms of ICS are available, but the relative effectiveness among ICSs has not been well investigated in published, randomized, controlled trials. The paucity of direct comparisons among ICS may have resulted in insufficient estimation in former systematic reviews/meta-analyses. To supplement the information on comparative effectiveness of ICS for pediatric asthma, we plan to conduct a network meta-analysis that will enable summary of direct and indirect evidence.

Methods and analysis: We will retrieve randomized, controlled trials that examined the effectiveness of ICS for pediatric asthma from the PubMed and Cochrane Central Register of Controlled Trials. After one author scans the title and abstract for eligible studies, two authors will independently review study data and assess the quality of the study. Studies of children (≤18 years old) with chronic asthma or recurrent wheezing episodes will be included if they used ICS for ≥4 weeks. We will define *a priory* core outcomes and supplemental outcomes of pediatric asthma, including exacerbation, healthcare use, and pulmonary function. Studies reporting a minimum of one core

For peer review only

outcome will be entered into the systematic review. After the systematic review is performed, extracted data of relevant studies will be synthesized in the Bayesian framework using the random effects model.

Ethics and dissemination: The results will be disseminated through peer-reviewed publications and conference presentations.

Protocol Registration: UMIN (000016724) and PROSPERO. (CRD42015025889)

Strengths and limitations of this study

- This study will be the first meta-analysis to examine comparative effectiveness of inhaled corticosteroids for pediatric asthma
- The results of this study will aid clinical decision making for practitioners and will provide the basis of future cost-effective analysis
- A potential limitation of our study is that it only includes published trials, which may be affected by some bias (e.g., publication bias)

For peer review only

INTRODUCTION

Morbidity of pediatric asthma is substantial worldwide. The prevalence of childhood asthma differs among countries(1), and up to 20–25% of children have prescriptions for anti-asthma medications in some industrialized countries(2, 3). Data from the USA represent an example of the asthma-related burden in children. These data show that, in 1 year, asthma causes exacerbations in 57% of pediatric patients, 12.8 million missed school days, 198,000 hospitalizations (the third cause of all childhood hospitalizations), and 185 deaths(1, 4).

Asthma is characterized by chronic inflammation of the airways(5). Therefore, for control of airway inflammation, regular maintenance therapy is required in most patients(6, 7). Inhaled corticosteroid (ICS) is the mainstream of asthma treatment in adults and children. ICS use achieves asthma control and this therapy leads to fewer exacerbations, emergency department visits, and hospitalizations(8). ICS also improves other outcome measures of asthma, such as pulmonary function(9) and quality of life (QOL) of patients(10).

There are several forms of ICSs for pediatric patients. Fluticasone propionate

For peer review only

(FP), hydrofluoroalkane-134a beclomethasone (HFA-BDP), budesonide (BUD), and ciclesonide are commonly prescribed ICSs for pediatric asthma(11). The relative effectiveness of these agents is estimated by their potency *in vitro*(12). Based on *in vitro* observations, the effectiveness of different ICSs is often assumed to be similar (i.e., 1:1 ratio in equivalent dose) to that *in vivo*. However, ICSs have different properties(8). FP has a potent affinity for steroid receptors with a long half-life(13), HFA-BDP is composed of small particles and can be delivered to small airways(14), and BUD suspension is easy to use in children who are not cooperative with inhalation therapy(15). Because of differences in formulations and delivery systems, the effectiveness of ICS can differ clinically(16). A medical database study from the USA reported that asthma control might be better in patients with HFA-BDP than in those with FP(17). However, few studies have compared different types of ICS directly(18). One systematic review concluded that there was little evidence of comparative effectiveness of ciclesonide with other ICSs among adult patients(19). This review was restricted to small, phase 2 studies of low power. The authors found only five randomized, controlled trials (RCTs) with a total of 84 patients(19).

For peer review only

One strategy to improve the statistical power of small studies is to conduct a meta-analysis(20). However, as mentioned above, studies comparing different classes of ICS are limited. The majority of clinical trials compared ICSs with other classes of drugs (e.g., antileukotrienes or ICS/long-acting beta-agonist [LABA] combination) or placebo. The paucity of trials of a direct comparison makes it difficult to perform a conventional meta-analysis (hereafter, we use the term "pairwise meta-analysis"). Recently, a novel meta-analytic technique called a network meta-analysis (NMA) was developed, and this enables results of trials to be combined in a direct and indirect manner(21-23).

In this context, we plan to conduct an NMA to address the following open question: Are there any differences in effectiveness among ICSs for pediatric asthma?

For peer review only

METHODS AND ANALYSIS

Goal of the study

We aimed to evaluate the comparative effectiveness of different ICSs for pediatric asthma. For this purpose, we will use the NMA approach to synthesize two types of clinical trials together: trials comparing different ICSs directly and trials comparing ICSs with other classes of intervention (e.g., antileukotrienes or placebo).

PRISMA-P 2015/PRISMA Extension Statement

For developing this protocol, we referred to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement(24), which is a guide for standard reporting of systematic review protocols. Corresponding to the PRISMA-P statement, we have registered this protocol at PROSPERO(25) and UMIN(26). Although we overall adhere to PRISMA-P statement, the method to deal with publication bias (item 16) is not specified in this protocol. This is because identification of publication bias is more complex in NMA owing to limited numbers of studies for each pairwise comparison, heterogeneity, and other limitations(27), and there are no

For peer review only

formal techniques to detect or assess the extent of publication bias. NMA is, however, a rapidly evolving research area and, if standard approaches will be established at the time of our final report, we are ready to use those skills.

We also referred to the PRISMA extension statement that incorporates reporting of NMA(27), and this protocol was partially developed with the help of the PRISMA extension statement.

Inclusion criteria: participants, interventions, comparisons, and outcomes

Participants

Studies of children (≤18 years old) with mild to moderate chronic or persistent asthma will be included. We will include studies exclusively comprising pediatric patients and those involving adult and pediatric patients if data of pediatric age groups are accessible and can be extracted.

This meta-analysis will also include studies of "children with recurrent wheeze" or "preschool wheezers". Currently, the diagnosis of asthma in young children is challenging because there are no universally accepted diagnostic criteria(28). Only a

For peer review only

subset of young children with recurrent wheezing episodes later develops physician-diagnosed asthma(29, 30). In addition, there is a wide range of differential diagnoses in recurrent wheeze that mimics pediatric asthma, such as cystic fibrosis, congenital malformation of the airways, and foreign body aspiration(31). Therefore, children with recurrent wheeze may or may not have asthma. The likelihood of asthma in such patients depends on the presence/absence of risk factors (e.g., family history)(32). Despite these problematic issues, we have decided to enroll children with recurrent wheeze for the following three reasons. First, recurrent wheezing is a major risk factor of asthma. As shown in studies of the Asthma Predictive Index, the combination of wheezing episodes (≥three episodes/year) and other criteria is strongly associated with the risk of asthma (up to 77% chance of active asthma)(30). Second, in addition to symptoms and risk factors, the therapeutic response is often important for diagnosis of pediatric asthma(32, 33) and empirical evidence indicates that children with recurrent wheeze may benefit from regular ICS use(31). Finally, previous systematic reviews/meta-analyses did not often distinguish children with asthma from those with recurrent wheeze(34). Because of these reasons, we consider that children

For peer review only

with asthma and those with recurrent wheeze share similar (although not identical) clinical characteristics and responses to ICS therapy. We will include only data of physician-diagnosed wheezing (≥3 times, separately) to ensure the consistency of patients' symptoms. In trials of children with recurrent wheeze, to ensure transversely assumption, we will carefully review (1) whether the risk factors of asthma (e.g., atopic status or family history) are described, and (2) whether differential diagnoses of wheeze are investigated. If these issues are insufficiently examined or documented, the authors will discuss whether such reports will be eligible for inclusion into the meta-analysis.

Interventions

We will include RCTs to examine the effectiveness of ICS in asthmatic children for ≥4 weeks. We will only include studies using ICS without co-interventions because the effectiveness of ICS is difficult to assess separately in trials with co-intervention (e.g., ICS/LABA combination therapy). We will limit studies evaluating the effectiveness of ICS in current use (i.e., studies of ICSs that are no longer used, such as HFA-chlorofluorocarbon, will be excluded). Therefore, this study will include the

For peer review only

beclomethasone dipropionate HFA-metered dose inhaler (MDI), BUD (dry powder inhaler [DPI] and nebules), ciclesonide (HFA-MDI), flunisolide (HFA-MDI), FP (HFA-MDI and DPI), and mometasone furoate (MDI and DPI).

Comparisons

This study will include clinical trials comparing one ICS with other active or inactive intervention(s), such as other types of ICSs, other classes of drugs (e.g., antileukotrienes), or placebo. The comparator should also be a single intervention because of the reason mentioned above.

Outcomes

In meta-analyses, researchers often declare the primary endpoint of the study(35). However, this practice is difficult in asthma studies(36). There are several domains in asthma control, such as a pulmonary function test or symptoms (e.g., exacerbation), and according to expert opinion, no single primary endpoint is recommended for assessment of responses to asthma(37). Therefore, our planned study will not define a single

For peer review only

primary endpoint, and instead, will examine different endpoints to determine a more complete understanding of asthma control by ICS (Table 1) (36).

For peer review only

Table 1: Core and Supplemental Outcomes relevant to Pediatric Asthma

	Core Outcomes	Supplemental Outcomes
Exacerbations	1. Systemic corticosteroids for asthma 2. Asthma-specific hospital admissions 3. Asthma-specific ED visits (separate UC visits when these can be differentiated) 4. Asthma-specific ICU admissions/ intubations 5. Death (all cause and asthma related)	(None defined for regular maintenance therapy)
Healthcare utilization	1. Asthma-specific hospital admissions 2. Asthma-specific ED visits 3. Asthma-specific outpatient visits 4. Asthma-specific detailed medication use (name, dose, and duration) 5. Resource use related to the intervention	1. Categorization of asthma-specific outpatient visits: • Primary care I. Scheduled II. Unscheduled • Specialty care I. Scheduled II. Unscheduled 2. Respiratory healthcare use 3. Asthma school absences 4. Asthma work presenteeism and absenteeism (WPAI instrument)

For peer review only

	Core Outcomes	Supplemental Outcomes
Pulmonary physiology	Spirometry (without bronchodilator)	1. PEF monitoring 2. Airway responsiveness 3. Lung volumes 4. Spirometry (prebronchodilator and postbronchodilator) 5. Gas exchange: arterial blood gases and pulse oximetry

ED: emergency department, UC unscheduled, WPAI: Work Productivity and Activity Impairment , PEF: peak flow

Based on Reference #49

For peer review only

Study outcomes should be clinically relevant, and ideally, they should be patient-centered(38). Additionally, outcomes should be used in a sufficiently large number of trials to be pooled in the analysis. Summarizing a large sample size would lead to more precise and confident estimation, and in NMA, combining small sample size studies could result in biased estimates(39). From these perspectives, we will not include studies that exclusively examined biomarkers, QOL, or severity scores for the following reasons. First, how these outcomes correlate with the clinical benefit has yet to be established, and the magnitude of benefit of these outcomes is difficult to interpret for patients and even for healthcare professionals(37). Second, a previous systematic review identified a few studies that examined these outcomes in pediatric patients(40). Finally, for QOL and severity scores, different formulations are available and they are not interchangeable with each other(41).

Exclusion criteria

We will exclude the following literature: abstracts only (e.g., conference paper), studies that are not on asthma (e.g., viral bronchiolitis), studies examining the dose–response

For peer review only

relationship of ICS (because of technical difficulties in incorporating data into the meta-analysis), safety assessment studies of ICS, and short-term or intermittent use of ICS.

Literature search

The primary literature search will rely on PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL). We will enroll all RCTs, including those of cross-over or quasi-randomized design, that are published in full-text articles in the English language. We will use medical subject headings and text words related to “child”, “asthma”, and “ICS” for the literature search(40). To ensure literature saturation, we will scan the reference lists of included studies or relevant reviews that are identified through the search

Selection of studies and extraction of data

One of the authors (MT) will scan the title and abstract of all of the literature that is retrieved by the initial search and select eligible articles for review of the full text. The

For peer review only

other two authors (HK and KT) will independently review full-text articles to assess eligibility and select citations to be meta-analyzed. Studies that reported at least one core outcome will be selected (shown in Table 1). The authors will also extract data independently using a prestandardized data abstraction form. Any disagreements will be resolved by discussion among all of the authors. The process of literature selection will be published (e.g., web-appendix style).

Quality assessment

We will assess the quality and risk of bias of eligible studies, ~~including~~ such as the method of randomization, treatment allocation concealment, blinding the outcome assessor, and dropouts. ~~The checklist prepared for RCTs~~ For this purpose, the Cochrane risk assessment tool will be used(42, 43). We will also rely on the Grading of Recommendations Assessment, Development and Evaluation approach for quality assessment in cumulative estimates.

Statistical methods

For peer review only

Figure 1a illustrates the scheme of the proposed pairwise meta-analysis. A pairwise meta-analysis can compare head-to-head trials (Fig. 1a, A vs B and A vs C), but cannot compare indirect arms (Fig. 1a, B vs C). In contrast, NMA can compare indirect arms (Fig. 1a, B vs C). Based on a "consistency assumption", the indirect effect B-C represents the difference between effect A-B and effect A-C (in this case, intervention A is referred to as a common comparator)(23, 44). Moreover, when there are head-to-head trials between B and C (Fig. 1b), NMA can combine the direct effect B-C and indirect effect B-C (i.e., effect A-B – effect A-C)(45). In this way, NMA combines all available evidence of direct and indirect comparisons. There is an additional strength in NMA. A pairwise meta-analysis can compare only two interventions at a time(23). In the situation shown in Fig. 1b, comparison of "A vs B vs C" is not feasible, even when direct comparisons exist. In contrast, NMA can compare ≥three interventions and determine which treatment works best. Further, NMA can compare more complex network loops (Fig. 2). Fig. 2 shows that comparative effectiveness among the ICSs' X, Y, and Z can be estimated by combining direct evidence (effect B-C) and indirect effects using drug A and placebo as common comparators. Based on these strengths in NMA,

For peer review only

we will evaluate comparative effectiveness of ICS by pooling the results from head-to-head trials of ICS and from indirect comparisons among different ICSs using placebo or other classes of medications (e.g., antileukotriene drugs) as a common comparator.

Statistical analyses will be conducted in a Bayesian hierarchical framework using a random effects model(46). We will use the gemtc package in R statistical software (47, 48). This package uses a method developed by Lu and Ades(22). This package also allows us to check for homogeneity and consistency, which are important assumptions in NMA that combined studies should be similar in clinical and statistical context (often referred to as transitivity assumption(23)). The statistical results will be presented in odds ratio (with credible interval) and probability ranking.

If we observe heterogeneity among studies, subgroup analyses will be conducted (see the subsection "Subgroup analysis" below). As an example of this situation, when the dosage of ICS varies considerably among studies, we will stratify studies of "low", "medium" and "high" dose(18, 49), and combine the results within each strata. The statistical analyses will be performed by one author (MT) on the basis

For peer review only

of previous expertise(50).

The gemtc R package has a unique function to check local (in)consistency and we will use this function for this purpose. We will use I^2 statistics to check global (in)consistency. This R package also prepares a function to generate network geometry, a graphical presentation of the network of evidence, which is an essential item of NMA reporting(27).

Subgroup analysis

Heterogeneity is a potential concern in meta-analysis. If heterogeneity is detected, we plan to conduct the following subgroup analyses and will report the results when necessary:

- Patients with chronic asthma vs recurrent wheezers
- Age groups stratified in three categories (0–4, 5–11, ≥12 years)
- Children-specific study vs "children and adult" study
- Dose stratification into low, medium, and high dose

For peer review only

Role of the funding source

This study is funded by the Japanese Society of Pediatric Allergy and Clinical Immunology. There is no role of the funding source in the study design, data collection and analysis, interpretation of results, or preparation and submission of the manuscript.

For peer review only

DISCUSSION

This protocol paper presents the hypothesis, rationale, and methodology of our planned study.

The relative potency of different ICSs has been the subject of considerable dispute and debate(12). Comparative dosing charts among ICSs have been proposed, (e.g., by an expert panel) (49) and they rely on comparative efficacy trials *in vitro*. Few studies have assessed relative therapeutic indices among ICSs(18, 51) and whether there are clinical differences among ICSs remains uncertain. To challenge this open question, we plan to conduct NMA, a newly developed meta-analytic technique.

NMA (also known as a multiple treatment comparison meta-analysis or mixed treatment meta-analysis) has gained popularity in recent years (23, 44), in light of comparative effectiveness research (CER). By definition, CER refers to studies that compare the benefits and harms of different interventions(52). The objectives of CER include helping physicians use existing treatments and treatment strategies more effectively(53). CER also aims to determine which interventions and strategies are most effective, safest, or least costly when multiple options are available(53). CER is an emerging research

For peer review only

area that is crucial for helping clinical decision making. However, within the current framework of medicine, limited data are available among different interventions. Comparative efficacy data are often lacking at preapproval and postapproval of medications (53 - 55). To bridge the gap between the needs and the lack of CER studies, new clinical trials or systematic reviews/meta-analyses, specifically NMA, are the priorities for future research(56). Our planned study to determine the comparative effectiveness of ICS for pediatric asthma is in line with the current effort for CER.

Relevance and credibility are two essential components in NMA(57). The expected results of our study will be relevant in that they will be applicable to clinical settings of interest to asthmatic patients or healthcare providers. We hope that the results in this NMA study will be credible, providing valid answers to the research question of "Are there any differences in effectiveness among ICSs for pediatric asthma?"

For peer review only

ETHICS AND DISSEMINATION

No ethical approval is required because this study will include published clinical trials with no personal data of patients.

The results of this study will be submitted to a peer-reviewed journal for publication and will also be presented at future conferences.

For peer review only

Authors' contributions

All authors made substantial contributions to the conception and design of the study. MT prepared the first draft of the article. HK, KT, and TI critically revised the manuscript for important intellectual content. All of the authors provided final approval of the version to be published.

Funding

This study is funded by the Japanese Society of Pediatric Allergy and Clinical Immunology.

Competing interests

No, there are no competing interests.

Data sharing

Additional data is available by emailing the corresponding author.

For peer review only

REFERENCES

1. Guilbert T, Moss HM, Lemanske RF Jr . Approach to Infants and Children with Asthma. In; Adkinson NF Jr, Bochner BS, Busse WW Holgate SH, Lemanske RF Jr, Simons FE, eds. Middleton's Allergy: Principles and Practice. Philadelphia; Saunders 2009: 1319-44

2. Bianchi M, Clavenna A, Labate L, Bortolotti A, Fortino I, Merlino L, et al. Anti-asthmatic drug prescriptions to an Italian paedriatic population. *Pediatr Allergy Immunol* 2009;20:585-91.

3. Bianchi M, Clavenna A, Bonati M. Inter-country variations in anti-asthmatic drug prescriptions for children. Systematic review of studies published during the 2000-2009 period. *Eur J Clin Pharmacol*. 2010;66:929-36.

4. Centers for Disease Control and Prevention. CDC vital signs: Asthma in the US 2011. Available from: http://www.cdc.gov/vitalsigns/pdf/2011-05-vitalsigns.pdf. [accessed 16 Mar 2015]

5. Hanania NA. Targeting airway inflammation in asthma: current and future therapies.

For peer review only

Chest. 2008;133:989-98.

6. Rank MA, Hagan JB, Park MA, Podjasek JC, Samant SA, Volcheck GW, et al. The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: a systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol*. 2013;131:724-9.

7. Morton RW, Everard ML, Elphick HE. Adherence in childhood asthma: the elephant in the room. *Arch Dis Child*. 2014;99:949-53.

8. Cerasoli F, Jr. Developing the ideal inhaled corticosteroid. *Chest*. 2006;130(1 Suppl):54S-64S.

9. Raissy HH, Kelly HW, Harkins M, Szefler SJ. Inhaled corticosteroids in lung diseases. *Am J Respir Crit Care Med*. 2013;187:798-803.

10. Murphy KR, Fitzpatrick S, Cruz-Rivera M, Miller CJ, Parasuraman B. Effects of budesonide inhalation suspension compared with cromolyn sodium nebulizer solution on health status and caregiver quality of life in childhood asthma. *Pediatrics*. 2003;112:e212-9.

11. The Thoracic Society of Australia and New Zealand. The Role of Corticosteroids in

For peer review only

the Management of Childhood Asthma. 2010. Available from: http://www.thoracic.org.au/imagesDB/wysiwyg/Steroidsinasthma_2010.pdf. [accessed 16 Mar 2015]

12. Barnes NC. The properties of inhaled corticosteroids: similarities and differences. *Prim Care Respir J*. 2007;16:149-54.

13. Derendorf H, Hochhaus G, Meibohm B, Mollmann H, Barth J. Pharmacokinetics and pharmacodynamics of inhaled corticosteroids. *J Allergy Clin Immunol*. 1998;101:S440-6.

14. Vanden Burgt JA, Busse WW, Martin RJ, Szefler SJ, Donnell D. Efficacy and safety overview of a new inhaled corticosteroid, QVAR (hydrofluoroalkane-beclomethasone extrafine inhalation aerosol), in asthma. *J Allergy Clin Immunol*. 2000;106:1209-26.

15. Szefler SJ, Eigen H. Budesonide inhalation suspension: a nebulized corticosteroid for persistent asthma. *J Allergy Clin Immunol*. 2002;109:730-42.

16. Baptist AP, Reddy RC. Inhaled corticosteroids for asthma: are they all the same? *J Clin Pharm Ther*. 2009;34:1-12.

17. Colice G, Martin RJ, Israel E, Roche N, Barnes N, Burden A, et al. Asthma

For peer review only

outcomes and costs of therapy with extrafine beclomethasone and fluticasone. *J Allergy Clin Immunol*. 2013;132:45-54.

18. Kelly HW. Comparison of inhaled corticosteroids: an update. *Ann Pharmacother*. 2009;43:519-27.

19. Dyer MJ, Halpin DM, Stein K. Inhaled ciclesonide versus inhaled budesonide or inhaled beclomethasone or inhaled fluticasone for chronic asthma in adults: a systematic review. *BMC Fam Pract*. 2006;7:34.

20. Thacker SB. Meta-analysis. A quantitative approach to research integration. *JAMA*. 1988;259:1685-9.

21. Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med*. 2002;21:2313-24.

22. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23:3105-24.

23. Cipriani A, Higgins JP, Geddes JR, Salanti G. Conceptual and technical challenges in network meta-analysis. *Ann Intern Med*. 2013;159:130-7.

24. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred

For peer review only

reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1.

25. University of York, Centre for Reviews and Dissemination. Available from: http://www.crd.york.ac.uk/PROSPERO/. [accessed 16 Mar 2015]

26. University hospital Medical Information Network (UMIN) Center. Available from: http://www.umin.ac.jp/. [in Japanese] [accessed 16 Mar 2015]

27. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C et. al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med.* 2015;162:777-84

28. Cave AJ, Atkinson LL. Asthma in preschool children: a review of the diagnostic challenges. *J Am Board Fam Med*. 2014;27:538-48.

29. Pescatore AM, Dogaru CM, Duembgen L, Silverman M, Gaillard EA, Spycher BD, et al. A simple asthma prediction tool for preschool children with wheeze or cough. *J Allergy Clin Immunol*. 2014;133:111-8. e13.

30. Castro-Rodriguez JA. The Asthma Predictive Index: a very useful tool for predicting

For peer review only

asthma in young children. *J Allergy Clin Immunol*. 2010;126:212-6.

31. Ducharme FM, Tse SM, Chauhan B. Diagnosis, management, and prognosis of preschool wheeze. *Lancet*. 2014;383:1593-6

32. Bacharier LB, Guilbert TW. Diagnosis and management of early asthma in preschool-aged children. J *Allergy Clin Immunol*. 2012;130:287-96;

33. Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Gotz M, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy*. 2008;63:5-34.

34. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics*. 2009;123:e519-25.

35. Rangwalla SC, Waljee AK, Higgins PD. Voting With their Feet (VWF) endpoint: a meta-analysis of an alternative endpoint in clinical trials, using 5-ASA induction studies in ulcerative colitis. *Inflamm Bowel Dis*. 2009;15:422-8.

36. Busse WW, Morgan WJ, Taggart V, Togias A. Asthma outcomes workshop: overview. *J Allergy Clin Immunol*. 2012;129(Suppl):S1-8.

For peer review only

37. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009;180:59-99.

38. Frank L, Basch E, Selby JV. The PCORI perspective on patient-centered outcomes research. *JAMA*. 2014;312:1513-4.

39. Dawn Odom CC, Beth Sherrill, Jianmin Wang, Bintu Sherif. Practical Issues When Conducting Network Meta-Analyses With a Limited Number of Studies [abstract]. ISPOR 19th Annual International Meeting; Montreal, QC, Canada2014.

40. Sinha IP, Williamson PR, Smyth RL. Outcomes in clinical trials of inhaled corticosteroids for children with asthma are narrowly focussed on short term disease activity. *PLoS One*. 2009;4:e6276.

41. Parulekar AD, Alobaidy A, Hanania NA. Asthma outcomes revisited. *Curr Opin Pulm Med*. 2013;19:6-12.

42. The Cochrane Collaboration's tool for assessing risk of bias. Available from: http://ohg.cochrane.org/sites/ohg.cochrane.org/files/uploads/Risk%20of%20bias%20ass

For peer review only

essment%20tool.pdf. [accessed 16 Mar 2015]

43. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.

44. Mills EJ, Thorlund K, Ioannidis JP. Demystifying trial networks and network meta-analysis. *BMJ*. 2013;346:f2914.

45. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ*. 2005;331:897-900.

46. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making*. 2013;33:607-17.

47. GeMTC R package. http://drugis.org/software/r-packages/gemtc [accessed 16 Mar 2015]

48. Neupane B, Richer D, Bonner AJ, Kibret T, Beyene J. Network meta-analysis using R: a review of currently available automated packages. *PLoS One*. 2014;9:e115065.

For peer review only

49. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *J Allergy Clin Immunol*. 2007;120(Suppl):S94-138.

50. Takeuchi M. Bayesian network meta-analysis suggests a similar effectiveness between a monovalent and a pentavalent rotavirus vaccine: a preliminary report of re-analyses of data from a Cochrane Database Systematic Review. *Hum Vaccin Immunother*. 2014;10:1421-4.

51. Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, et al. Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta2 agonists for the treatment of chronic asthma in children under the age of 12 years. *Health Technol Assess*. 2008;12:1-174.

52. Sox HC. Defining comparative effectiveness research: the importance of getting it right. *Med Care*. 2010;48(Suppl):S7-8.

53. Hochman M, McCormick D. Characteristics of published comparative effectiveness studies of medications. *JAMA*. 2010;303:951-8.

54. Goldberg NH, Schneeweiss S, Kowal MK, Gagne JJ. Availability of comparative

For peer review only

efficacy data at the time of drug approval in the United States. *JAMA*. 2011;305:1786-9.

55. Thomas RH, Freeman MK, Hughes PJ. Preapproval and postapproval availability of published comparative efficacy research on biological agents. *Am J Health Syst Pharm*. 2013;70:1250-5.

56. Li T, Vedula SS, Scherer R, Dickersin K. What comparative effectiveness research is needed? A framework for using guidelines and systematic reviews to identify evidence gaps and research priorities. *Ann Intern Med*. 2012;156:367-77.

57. Jansen JP, Trikalinos T, Cappelleri JC, Daw J, Andes S, Eldessouki R, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health*. 2014;17:157-73.

For peer review only

Figure legends

Figure 1a: Scheme for pairwise meta-analysis. In this example, comparison of "B vs. C" is impractical.

Figure 1b: Scheme for pairwise and network (indirect) meta-analysis. An indirect comparison of "B vs. C" can be estimated from knowledge of "A vs. B" and "A vs. C" trials.

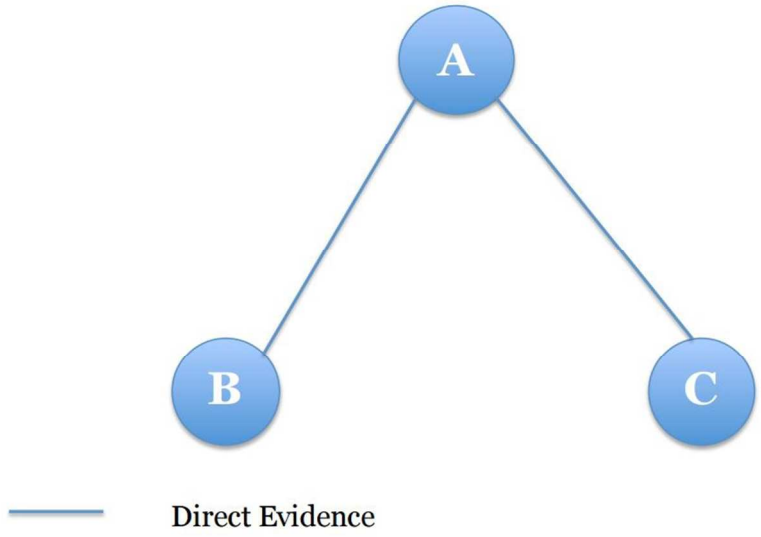
Figure 2: Scheme for a complex network in network meta-analysis.

NMA: network meta-analysis.

Amendments

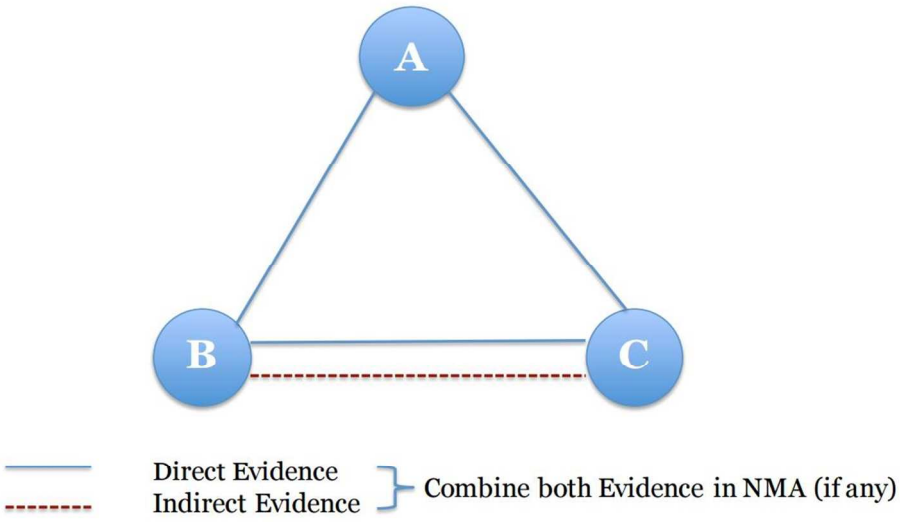
Important protocol amendments will be published through the registered sites of this protocol.

For peer review only



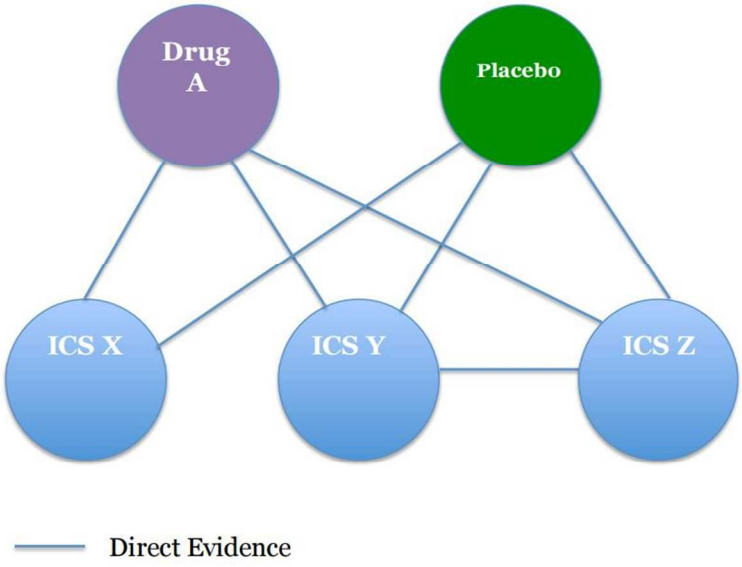
288x182mm (96 x 96 DPI)

eview only



317x191mm (96 x 96 DPI)

For peer review only



283x195mm (96 x 96 DPI)

view only

Supplementary File – search strategy

#1 asthma:ti,ab,kw

#2 (antiasthma OR anti-asthma):ti,ab,kw

#3 wheez*:ti,ab,kw

#4 (bronch?spas* OR bronchoconstric* OR bronchismus OR bronchiospas*):ti,ab,kw

#5 cough:ti,ab,kw

#6 (#1 OR #2 OR #3 OR #4 OR #5)

#7 (child*):ti,ab,kw

#8 (paediatric* OR pediatric):ti,ab,kw

#9 (infan*):ti,ab,kw #10 (young*):ti,ab,kw

#11 (toddler*):ti,ab,kw

#12 bab*:ti,ab,kw

#13 (preschool or pre-school):ti,ab,kw

#14 (teenage*):ti,ab,kw #15 (adolesce*):ti,ab,kw

#16 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)

#17 beclomethasone:ti,ab,kw

#18 fluticasone:ti,ab,kw

#19 budesonide:ti,ab,kw

#20 flunisolide:ti,ab,kw

#21 mometasone:ti,ab,kw

#22 ciclesonide:ti,ab,kw

#23 (corticosteroid* OR *corticoid*):ti,ab,kw

#24 (inhaled *steroid*):ti,ab,kw

#25 (qvar or beclovent or flixotide or flovent or pulmicort or aerobid or asmanex or alvesco):ti,ab,kw

#26 (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #27)

#27 (#6 AND #16 AND #26)

For peer review only

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item (# of relevant page/not applicable *etc.*)
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review (p.1)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such (NA)
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number (p.4)
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author (p.1)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review (p.25)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments (p.36)
Support:		
Sources	5a	Indicate sources of financial or other support for the review (p.21)
Sponsor	5b	Provide name for the review funder and/or sponsor (NA)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol (NA)
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known (p.6-8)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) (p.8)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review (p.10-15)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage (p.16)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated (attachment file)
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review (p.16-17)

For peer review only

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) (p.16-17)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators (p.16-17)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications (p.14-15)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale (Table 1)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis (p.17)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised (p.17-19)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) (p.17-20)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) (p.20)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned (NA)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) (p.10)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) (p.17)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

For peer review only