Treatment dose increase versus comedication in allergic rhinitis: Systematic review with dose-response network meta-analysis protocol

Aumento da dose versus comedicação na rinite alérgica: Protocolo de revisão sistemática com meta-análise em rede dose-resposta

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ABSTRACT

Background: In patients with allergic rhinitis who remain uncontrolled despite being treated with standard daily doses of a single medication, strategies that can be followed to achieve adequate symptom control include (i) increasing the medication dose, or (ii) adding an additional medication (co-medication). However, it is not known which one of these two strategies is more effective. **Objectives:** This article describes a protocol of a systematic review with dose-response network meta-analysis aiming at comparing different intranasal and oral medications in patients with seasonal or perennial allergic rhinitis. **Methods:** We will search four electronic bibliographic databases and three clinical trials databases for randomized controlled trials (i) assessing adults or children with seasonal or perennial allergic rhinitis, and (ii) evaluating the effect of intranasal medications, oral medications or combinations of any intranasal and/or oral medications for allergic rhinitis. Assessed outcomes will include the Total Nasal Symptom Score, the Total Ocular Symptom Score and the Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ). We will assess the methodological quality of included primary studies by using the Cochrane risk-of-bias tool. Certainty in the body of evidence for the analysed outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation approach for network meta-analyses (GRADE-NMA). We will perform a frequentist dose-response model-based network meta-analysis. Sensitivity analyses will be performed by separately analysing data for seasonal and perennial allergic rhinitis. **Conclusion:** This protocol describes the methodology of a systematic review that will fit dose-response network meta-analysis models in the comparison between different intranasal and oral medications. The findings of this systematic review will support recommendations in the Allergic Rhinitis and its Impact on Asthma (ARIA) 2024-2025 guidelines.

Keywords: *Allergic rhinitis, network meta-analysis, intranasal corticosteroids, oral antihistamines.*

RESUMO

Fundamentos: *Em pacientes com rinite alérgica que se mantêm sintomáticos não obstante tratamento com doses diárias padrão de uma medicação única, existem algumas estratégias que podem ser seguidas para assegurar um controlo adequado dos sintomas. Essas estratégias incluem: aumento da dose medicamentosa ou adição de mais um medicamento (comedicação). No entanto, desconhece-se qual destas duas estratégias é mais eficaz.* ***Objetivos:*** *Este artigo corresponde a um protocolo de uma revisão sistemática com meta-análise em rede dose-resposta com o objetivo de comparar diferentes medicamentos intranasais e orais em doentes com rinite alérgica sazonal ou perene.* ***Métodos:*** *Serão pesquisadas quatro bases bibliográficas eletrónicas e três bases de registos de ensaios clínicos. Serão incluídos ensaios clínicos aleatorizados que avaliam o efeito de medicamentos intranasais ou orais (ou combinações de medicamentos intra-nasais e/ou orais) em adultos ou crianças com rinite alérgica sazonal ou perene. Os* outcomes *a avaliar incluem o* score *total de sintomas nasais, o* score *total de sintomas oculares e o questionário de qualidade de vida de rinoconjuntivite. A qualidade metodológica dos estudos primários incluídos será avaliada através da ferramenta de risco de viés da Cochrane. A certeza na evidência será avaliada usando o* Grading of recommendations assessment, develop-

ment and evaluation approach for network meta-analyses *(GRADE-NMA). Procederemos a meta-análise em rede com modelos dose-resposta. Serão feitas análises de sensibilidade ao analisar separadamente dados de estudos em rinite alérgica sazonal e perene.* ***Conclusões:*** *Este protocolo descreve a metodologia de uma revisão sistemática que aplicará modelos de meta-análise em rede dose-resposta na comparação entre diferentes medicamentos intranasais e orais. As conclusões desta revisão sistemática irão informar as recomendações das* guidelines Allergic rhinitis and its impact on asthma *2024-2025.*

Palavras-chave: *Anti-histamínicos orais, corticosteróides intranasais, meta-análise em rede, rinite alérgica.*

INTRODUCTION

Allergic rhinitis (AR) is a prevalent chronic disease whose symptoms can have a substantial deleterious impact on work productivity, school performance, and quality of life(1-3). The treatment for AR mostly involves the use of medications registered for use in a single dose, and, in contradistinction to urticaria, AR guidelines do not have recommendations on increasing the dose of medications.

In AR, recent systematic reviews have compared different individual intranasal and oral medications to identify the most efficacious ones in controlling nasal and ocular symptoms and in improving quality of life(4-9). Nevertheless, there are patients whose symptoms remain uncontrolled despite being treated with standard daily doses of a single medication. In these patients, several options can be considered to achieve an adequate symptom control, including – among others – increasing the medication dose or adding an additional medication (i.e., resorting to co-medication). It is not known, however, which one of these two strategies is more effective, as previous systematic reviews on AR treatments have not explored the impact of differences in doses within each treatment, despite that being of the utmost importance (e.g., MASK-air mHealth studies have reported that when unsatisfied with their treatments, patients frequently resort to comedication(10,11)). In fact, the employed meta-analytical methods have important limitations in dealing with different doses of the same medication. By contrast, dose-response model-based network meta-analyses (NMA) can be used to compare different interventions while adequately fitting dose-response relationships for their different doses(12).

This article describes the protocol of a systematic review with dose-response NMA with the aim of comparing different intranasal and oral medications in patients with seasonal or perennial AR. In particular, we will synthesise all evidence from randomised controlled trials (RCTs) on the efficacy of these medications in improving nasal symptoms, ocular symptoms, and rhinoconjunctivitis-related quality of life. Medication safety will be evaluated as a secondary endpoint. This systematic review will inform the Allergic Rhinitis and its Impact on Asthma (ARIA) 2024-2025 guidelines(13), particularly the question "Should comedication vs. medication updosing be used in patients with allergic rhinitis that is poorly controlled despite pharmacologic treatment?"(14).

METHODS

We will perform a systematic review with dose-response NMA of RCTs evaluating intranasal or oral medications in patients with AR. This systematic review will follow the Preferred Reporting Items for Systematic Re-

views and Meta-Analyses (PRISMA) extension for NMA (PRISMA-NMA)(15). Its protocol has been registered in PROSPERO (CRD420251113186).

ELIGIBILITY CRITERIA

We will include RCTs with a parallel design assessing patients of any age with seasonal or perennial AR and evaluating the effect of (i) intranasal medications (intranasal corticosteroids, intranasal antihistamines, or fixed combinations of intranasal antihistamines + corticosteroids), (ii) oral medications (oral antihistamines or antileukotriene receptor antagonists), or (iii) combinations of any intranasal and/or oral medications for AR. We will consider both studies in which these interventions are compared with placebo as well as those in which active interventions are compared among themselves.

In line with the outcomes prioritized by the ARIA 2024-2025 guideline panel(13,16), we will include studies reporting results on at least one of the following patient-reported outcome measures: Total Nasal Symptom Score (TNSS), Total Ocular Symptom Score (TOSS), or Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). We define the TNSS as any score computed based on the sum of four patient-reported scores for individual nasal symptoms (sneezing, nasal itching, rhinorrhea, and nasal congestion), and the TOSS as any score computed based on the sum of three patient-reported scores for individual ocular symptoms (ocular itching, ocular redness and ocular watering/tearing). We will consider the TNSS, TOSS, and RQLQ assessed in a reflective manner; that is, reflecting patients' symptoms in the previous 12 or 24 hours. Considering Food and Drug Administration recommendations, we will only include RCTs with a follow-up period of at least 2 weeks if assessing patients with seasonal AR or at least 4 weeks if assessing patients with perennial AR(17).

We will not exclude studies based on publication language, date, or status (i.e., we will include relevant studies irrespective of whether they were published as full papers, conference abstracts, clinical trials registries, or others).

INFORMATION SOURCES AND SEARCH STRATEGY

We will include the primary studies that have been included in our previous systematic reviews and that meet the eligibility criteria(4-9). In brief, we have conducted six previous systematic reviews in which we searched for RCTs evaluating intranasal(4-6,8) or oral medications(4,7,9) in patients with seasonal or perennial AR. The information sources and search strategies for these systematic reviews are described in the respective publications(4-9). In detail, we searched four bibliographic databases (MEDLINE and Embase via Ovid, Web of Science, and the Cochrane Central Register of Controlled Trials) as well as databases of clinical trials (clinicaltrials.gov, the GSK clinical study dataset, and the Astra Zeneca Clinical Trials Website). We will update our search considering the same information sources and using a search strategy based on the ones adopted in our previous systematic reviews (Supplementary Table 1).

STUDY SELECTION AND DATA COLLECTION

In our previous systematic reviews, each record has been independently reviewed by two researchers for eligibility and data extraction. Accordingly, two researchers will independently evaluate each record resulting from the search update. In detail, records will first be evaluated by title and abstract screening, and then by full-text reading. Any non-excluded record will be assessed to determine whether multiple publications originated from the same study.

The following variables will be independently extracted by two reviewers from each newly included primary

Table 1. Standard daily doses in adult patients that will be considered for the different individual medications a

Medication	Standard daily dose of active compounds
Azelastine (intranasal)	560 µg
Azelastine-fluticasone (intranasal)	748 µg
Beclomethasone (intranasal)	320 µg
Bilastine (oral)	20 mg
Budesonide (intranasal)	256 µg
Cetirizine (oral)	10 mg
Ciclesonide (intranasal)	200 µg
Desloratadine (oral)	5 mg
Ebastine (oral)	10 mg
Fexofenadine (oral)	180 mg
Fluticasone furoate (intranasal)	110 µg
Fluticasone propionate (intranasal)	200 µg
Levocetirizine (oral)	5 mg
Loratadine (oral)	10 mg
Mometasone (intranasal)	200 µg
Montelukast (oral)	10 mg
Olopatadine (intranasal)	5320 µg
Olopatadine-mometasone (intranasal)	5520 µg
Rupatadine (oral)	10 mg
Terfenadine (oral)	120 mg
Triamcinolone (intranasal)	220 µg

[a] Doses defined based on the literature (i.e., doses most commonly evaluated in randomized controlled trials) and after discussion with allergists.

study: (i) the assessed disease (seasonal or perennial AR), (ii) the participants' eligibility criteria, (iii) the data collection period, (iv) the places from where patients were recruited, (v) the follow-up period, (vi) the assessed medications, (vii) the total daily dose of medications, (viii) the number of randomized participants, (ix) the number of participants completing the study, (x) the participants' age and sex distribution, and (xi) the assessed outcomes. For each desirable effect outcome (TNSS, TOSS, and/or RQLQ), we will retrieve (i) information on the scale and computation methods, as well as (ii) baseline values and post-intervention and/or change from baseline values. We will also retrieve information on undesirable outcomes, namely on the frequency of patients (i) developing at least one adverse event (AE) (as defined by the authors), (ii) developing at least one serious AE, and (iii) discontinuing treatment due to AE. In case results are only provided in a graphical form (rather than numerical data in text form), estimates will be obtained using the Plot-Digitizer tool.

Disagreements between reviewers in the data selection or extraction processes will be resolved by consensus or by a third reviewer.

RISK OF BIAS AND CRITICAL APPRAISAL OF THE EVIDENCE

In our previous systematic reviews, the risk of bias of each included primary study was independently evaluated (at an outcome level) by two researchers using the Cochrane risk-of-bias tool(18). The same procedure will be followed for newly included primary studies. Disagreements will be resolved by consensus or by a third reviewer.

We will evaluate the certainty of the evidence at an outcome level using the GRADE approach for NMA(19,20). As starting points for our judgements on the different domains, we will use an automated tool developed by our team (under testing by the GRADE Working Group). This tool follows the most recent GRADE guidance(21), particularly in terms of considering predefined decision thresholds to judge limitations in the design or execution of studies ("risk of bias"), inconsistency, and imprecision. For continuous outcomes, we will consider that standardized mean differences of 0.2, 0.5, and 0.8 can be used as decision thresholds, respectively distinguishing "trivial or none" from "small" effects, "small" from "moderate" ef-

fects, and "moderate" from "large" effects. These thresholds have been classically used to contextualize standardized mean differences(22) and will also allow us to judge effects based not only on "significance" criteria but also in terms of effect sizes for a clinical audience. For dichotomous outcomes, we will consider previously determined decision thresholds for AEs(23).

QUANTITATIVE SYNTHESIS OF THE EVIDENCE

Desirable outcomes are continuous and will be presented as mean (± standard deviation) baseline and change-from-baseline values. When information on spread measures is missing, we will estimate them based on an approach proposed by Weir *et al.*(24) as described and applied in our previous systematic reviews(4-9). Undesirable outcomes are dichotomous and will be presented using absolute and relative frequencies.

Dose-response network meta-analysis

We will perform a frequentist dose-response model-based NMA(12). For desirable effects outcomes (TNSS, TOSS, and RQLQ), we will perform a random-effects NMA of mean differences in change-from-baseline values. For undesirable effects outcomes (AE, withdrawal due to AE), we will perform a random-effects NMA of risk ratios.

We will perform a dose-response NMA so that we can estimate a dose-response relationship for different doses of AR medications. All analyses will be performed at an individual medication level, considering the whole range of daily doses that have been evaluated for each medication. Considering that most medications have only been evaluated on a limited set of daily doses, we will fit linear dose-response models (i.e., such limited evidence may render it more difficult to have evidence supporting the application of more complex models).

We will evaluate the comparative effect of individual medications per unit of standard daily medication dose. For example, for loratadine, adults are usually treated with a daily dose of 10 mg. Therefore, 10 mg corresponds to the standard daily medication dose for loratadine (and would be coded as "1" in our models); a study evaluating a dose of 20 mg would be assessing two times the standard daily medication dose for loratadine (such a dose would be coded as "2" in our models) (Figure 1). On the other hand, adults are usually treated with 200 µg of fluticasone propionate, so this will be considered the standard daily dose for this medication. The list of standard daily doses that we will consider in our systematic review is displayed in Table 1. The justification for considering units of standard daily medication doses is grounded on the dose differences in intranasal medications (typically daily doses of tens to hundreds of micrograms of active compound) *vis-à-vis* oral medications (typically daily doses of tens to hundreds of milligrams). Considering standard daily medication doses will then allow for enhanced comparability in results presentation.

Whenever dealing with interventions corresponding to non-fixed co-medication schemes, we will consider the standard daily dose of one of the medications that are part of such a co-medication scheme. For example, an intervention corresponding to 10 mg of loratadine + 5 mg of montelukast will not be coded as corresponding to a daily dose of 1.5 (1 standard daily dose of loratadine + 0.5 standard daily dose of montelukast) but rather – in different models – as 1 and 0.5. Coding as "1" will inform if increasing the dose of loratadine is more or less effective than adding montelukast (Figure 1); coding as "0.5" will inform if increasing the dose of montelukast is more or less effective than adding loratadine.

We will consider oral "placebo" as our reference category, assuming a dose of 0 for placebo interventions. Considering preliminary evidence suggesting relevant differences between nasal and oral placebo (under review), we will attempt to distinguish between nasal and oral placebo, setting nasal placebo as an intervention always coded as "1"

Our main analysis will only consider studies performed in adults, but will evaluate together studies in perennial

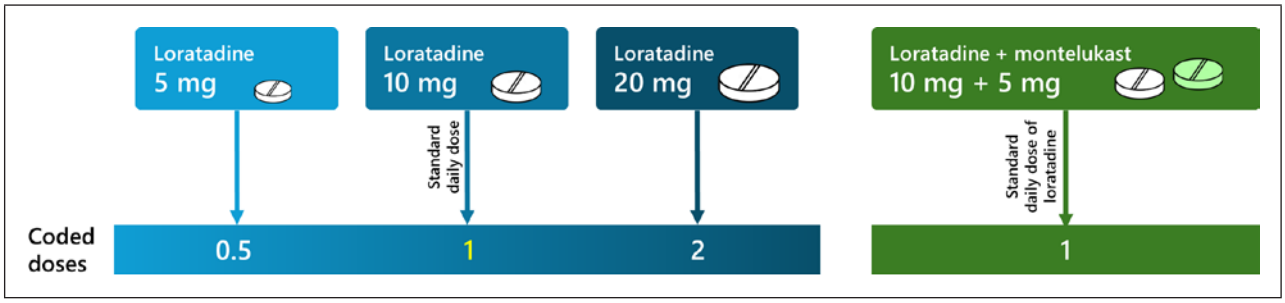

Figure 1. Diagram representing the process for coding the doses of medications based on the standard daily doses (example of loratadine)

and seasonal AR. Subgroup analyses will be performed for studies evaluating patients with perennial and seasonal AR. An additional separate analysis will be performed for studies assessing children. This separate analysis is justified by the fact that standard daily doses are different in children and in adults.

The transitivity assumption (i.e., the existence of comparable distributions of patient characteristics across studies in the treatment network) will be assessed by considering patient and study characteristics across the studies that compare pairs of treatments. We will assess heterogeneity by evaluating the I^2 statistic and by comparing the number of decision thresholds crossed by the random-effects *versus* the fixed-effects model. An $I^2 \geq 50\%$ will be considered to represent substantial heterogeneity.

We will present results using net league tables, dose-response plots, and plots displaying the probability that an intervention in co-medication (standard-daily dose + additional medication) is more efficacious than when given alone for a wide range of doses. All analyses will be performed using the software R. The netdose package will be used for dose-response network meta-analysis.

DISCUSSION

This systematic review with dose-response NMA will not only compare different individual interventions used for the treatment of AR – including intranasal medications, oral medications and non-fixed combinations – but also evaluate whether it is more efficacious to increase the treatment dose or to add an additional medication. It is likely that there will be different conclusions depending on the medications being considered. That is, for some treatments, updosing may be more efficacious, while for others, better results may be achieved with co-medication. Our systematic review will take that aspect into account by informing on the best strategy on a per medication level, so that it may support more nuanced recommendations by distinguishing when updosing may outperform co-medication and vice-versa.

In poorly controlled patients with AR, switching medications can potentially result in symptom improvement. For example, a previous systematic review has shown that intranasal medications tend to be more efficacious and as safe as oral treatments(8). However, in patients taking oral medications, switching to an intranasal formulation may not always be possible. Some patients may have corticosteroid-phobia or may have a strong preference for oral interventions. On the other hand, despite intranasal treatments being generally more efficacious, not all patients achieve an adequate disease control with a single medication given in a standard daily dose. Overall, this points to the clinical importance of understanding the gains and risks associated with increasing the dose of a certain AR treatment *vis-à-vis* adding an additional medication. Of note, while this systematic review aims to inform on the desirable and un-

desirable effects (i.e., benefits and harms) associated with these two strategies, there are other aspects that should be considered in the decision-making process, including the adherence, costs and planetary health impact of both strategies(25-27). These criteria will be the subject of future studies, particularly using data from MASK-air, a survey to experts on medication costs, and life cycle assessments of medications.

From a methodological point of view, this systematic review will, to the best of our knowledge, be the first dose-response NMA in the field of allergy. We expect to develop methodologically innovative ways of presenting results, considering not only whether differences are "statistically significant", but also the probability of different strategies being better than others, including consideration of decision thresholds.

In conclusion, this systematic review will fit dose-response NMA models in the comparison between different intranasal and oral medications, providing results on a per-medication level. The findings of this systematic review will support recommendations in the ARIA 2024-2025 guidelines, particularly regarding the desirable and undesirable effects related to the question of the comparison between medication updosing *vs.* co-medication.

Conflict of interest

JAF reports grants from Astrazeneca and Mundipharma; and personal fees from AstraZeneca, Mundipharma, Sanofi, GSK and Teva, outside the submitted work.

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REFERENCES

1. Vieira RJ, Azevedo LF, Pereira AM, *et al.* Impact of Allergic Rhinitis Control on Work Productivity and Costs: A Real-World Data MASK-air Study. J Allergy Clin Immunol Pract Nov 2024;12(11):3107-3115 e13. doi:10.1016/j.jaip.2024.07.026.
2. Vieira RJ, Leemann L, Briggs A, *et al.* Poor Rhinitis and Asthma Control Is Associated With Decreased Health-Related Quality of Life and Utilities: A MASK-air Study. J Allergy Clin Immunol Pract Jun 2024;12(6):1530-8 e6. doi:10.1016/j.jaip.2024.03.036.
3. Vieira RJ, Pham-Thi N, Anto JM, *et al.* Academic Productivity of Young People With Allergic Rhinitis: A MASK-air Study. J Allergy Clin Immunol Pract Nov 2022;10(11):3008-17 e4. doi:10.1016/j.jaip.2022.08.015.
4. Gil-Mata S, Vieira RJ, Borowiack E, *et al.* Intranasal treatments for allergic rhinitis in preschool- and school-aged children: network meta-analysis. J Allergy Clin Immunol Pract Jul 15 2025;doi:10.1016/j.jaip.2025.07.004

5. Sousa-Pinto B, Vieira RJ, Bognanni A, *et al.* Efficacy and safety of intranasal medications for allergic rhinitis: Network meta-analysis. Allergy Jan 2025;80(1):94-105. doi:10.1111/all.16384.
6. Sousa-Pinto B, Vieira RJ, Brozek J, *et al.* Intranasal antihistamines and corticosteroids in allergic rhinitis: A systematic review and meta-analysis. J Allergy Clin Immunol Aug 2024;154(2):340-54. doi:10.1016/j.jaci.2024.04.016.
7. Thomander T, Gil-Mata S, Riera-Serra P, Vieira RJ, Ferreira A, Bognanni A, *et al.* Efficacy and safety of oral treatments for allergic rhinitis in children: A systematic review and network meta-analysis (Under Review).
8. Torres MI, Gil-Mata S, Bognanni A, *et al.* Intranasal Versus Oral Treatments for allergic rhinitis: A systematic review with meta-analysis. J Allergy Clin Immunol Pract Dec 2024;12(12):3404-3418. doi:10.1016/j.jaip.2024.09.001.
9. Vieira RJ, Gil-Mata S, Ferreira A, Riera-Serra P, Bognanni A. Duarte VH, *et al.* Efficacy and safety of oral antihistamines for allergic rhinitis: Network meta-analysis (Under review).
10. Sousa-Pinto B, Sa-Sousa A, Vieira RJ, *et al.* Behavioural patterns in allergic rhinitis medication in Europe: A study using MASK-air((R)) real-world data. Allergy Sep 2022;77(9):2699-2711. doi:10.1111/all.15275.
11. Sousa-Pinto B, Vieira RJ, Bognanni A, Martini M, Ordak M, Paoletti G. Comparison of allergic rhinitis treatments on patient satisfaction: A MASK-air® and EAACI Methodological Committee Report. Allergy 2025.
12. Pedder H, Dias S, Bennetts M, Boucher M, Welton NJ. Joining the dots: Linking disconnected networks of evidence using dose-response model-based network meta-analysis. Med Decis Making Feb 2021;41(2):194-208. doi:10.1177/0272989X20983315.
13. Bousquet J, Schunemann HJ, Sousa-Pinto B, *et al.* Concepts for the development of person-centered, digitally enabled, artificial intelligence-assisted ARIA care pathways (ARIA 2024). J Allergy Clin Immunol Pract Oct 2024;12(10):2648-2668 e2. doi:10.1016/j.jaip.2024.06.040.
14. Sousa-Pinto B, Vieira RJ, Marques-Cruz M, *et al.* Artificial intelligence-supported development of health guideline questions. Ann Intern Med Nov 2024;177(11):1518-29. doi:10.7326/ANNALS-24-00363.
15. Hutton B, Salanti G, Caldwell DM, *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 Jun 2 2015;162(11):777-84. doi:10.7326/M14-2385.
16. Bousquet J, Sousa-Pinto B, Vieira RJ, Schunemann H, Zuberbier T, Bognanni A. Methodology for the development of the allergic rhinitis and its impact on asthma (ARIA) 2024-2025 guidelines: From Evidence-to-Decision frameworks to digitalised shared decision-making algorithms.
17. Food and Drug Administration. Allergic Rhinitis: Developing Drug Products for Treatment - Guidance for Industry. 2018. https://www.fda.gov/files/drugs/published/Allergic-Rhinitis--Developing-Drug-Products-for-Treatment-Guidance-for-Industry.pdf.
18. Higgins JP, Altman DG, Gotzsche PC, *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ Oct 18 2011;343:d5928. doi:10.1136/bmj.d5928.
19. Brignardello-Petersen R, Florez ID, Izcovich A, *et al.* GRADE approach to drawing conclusions from a network meta-analysis using a minimally contextualised framework. BMJ Nov 11 2020;371:m3900. doi:10.1136/bmj.m3900.
20. Brignardello-Petersen R, Izcovich A, Rochwerg B, *et al.* GRADE approach to drawing conclusions from a network meta-analysis using a partially contextualised framework. BMJ Nov 10 2020;371:m3907. doi:10.1136/bmj.m3907.
21. The GRADE Working Group. The GRADE Book version 1.0 (updated September 2024).
22. Cohen J. Statistical power analysis for the behavioral sciences. routledge; 2013.
23. Sousa-Pinto B, Bognanni A, Gil-Mata S, *et al.* Empirical estimation of disutilities and decision thresholds for composite endpoints. *J Clin Epidemiol*. Mar 2025;179:111638. doi:10.1016/j.jclinepi.2024.111638.
24. Weir CJ, Butcher I, Assi V, *et al.* Dealing with missing standard deviation and mean values in meta-analysis of continuous outcomes: a systematic review. BMC Med Res Methodol Mar 7 2018;18(1):25. doi:10.1186/s12874-018-0483-0.
25. Alonso-Coello P, Oxman AD, Moberg J, *et al.* GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. BMJ Jun 30 2016;353:i2089. doi:10.1136/bmj.i2089.
26. Alonso-Coello P, Schunemann HJ, Moberg J, *et al.* GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ Jun 28 2016;353:i2016. doi:10.1136/bmj.i2016.
27. Vieira RJ, Sousa-Pinto B, Herrmann A, *et al.* A novel approach to consider Planetary Health in guideline development: a GRADE approach using the Allergic Rhinitis and its Impact on Asthma (ARIA) 2024-2025 guidelines as a case-study. J Allergy Clin Immunol Pract Jun 10 2025;doi:10.1016/j.jaip.2025.04.060.