Methodology for the Global Initiative for Asthma (GINA) Strategy Report 2023

GINA SCIENCE COMMITTEE

The GINA Science Committee was established in 2002 to review published research on asthma management and prevention, to evaluate the impact of this research on recommendations in GINA documents including the *GINA Global Strategy for Asthma Management and Prevention* (the Strategy Report), and to provide yearly updates to these documents. The members are recognized leaders in asthma research and clinical practice, with the necessary scientific expertise to contribute to the task of the Committee. They are invited to serve for a limited period and in a voluntary capacity. The Committee is broadly representative of adult and pediatric disciplines, and members are drawn from diverse geographic regions. The Committee normally meets in person three times a year, including at meetings held in conjunction with the international conferences of the American Thoracic Society and European Respiratory Society, to review asthma-related scientific literature and discuss topics of relevance to asthma. During COVID-19, meetings of the Committee were held online each month. Statements of interest for Committee members are found on the GINA website www.ginasthma.org.

PROCESSES FOR UPDATES AND REVISIONS OF THE GINA STRATEGY REPORT

Literature search

Two PubMed searches are performed each year, each covering the previous 18 months, using filters established by the Science Committee. The search terms include asthma, all ages, only items with abstracts, clinical trial or meta-analysis or systematic review, and human (Table 1). The search is not limited to specific PICOT (Population, Intervention, Comparison, Outcomes, Time) questions. The 'clinical trial' publication type includes not only conventional randomized controlled trials, but also pragmatic, real-life and observational studies. The search for systematic reviews includes, but is not limited to, those conducted using GRADE methodology.[1] An additional search is conducted to identify clinical practice guideline documents published by other international organizations. The respiratory community is also invited to submit any other fully published peer-reviewed articles for consideration, provided that the full paper is submitted in (or translated into) English; however, because of the comprehensive process for literature review, such *ad hoc* submissions have rarely resulted in substantial changes to the report.

Table 1. Search strategy

1. Clinical trials	("asthma"[MeSH Terms] OR "asthma"[TIAB]) AND (Clinical Trial[ptyp] OR random*[TIAB]) AND hasabstract[text] AND ("[*Relevant date*]"[PDAT]: "[*Relevant date*]"[PDAT]) NOT Clinical Trial, Phase I[ptyp] NOT Clinical Trial, Phase II[ptyp]
2. Meta-analyses and systematic reviews	("asthma"[MeSH Terms] OR "asthma"[TIAB]) AND (Meta-Analysis[ptyp] OR meta-analysis[TIAB] OR "systematic review"[ptyp] OR "systematic review"[TIAB]) AND hasabstract[text] AND ("[*Relevant date*]"[PDAT] : "[*Relevant date*]"[PDAT]

[1] Schunemann HJ, Jaeschke R, Cook DJ, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. Am J Respir Crit Care Med 2006; 174: 605-614.

Systematic reviews

Unique among evidence-based recommendations in asthma, and most other therapeutic areas, GINA conducts an ongoing twice-yearly update of the evidence base for its recommendations. GINA does not carry out or commission its own GRADE-based reviews, because of the large number of PICOT questions that would be necessary for a comprehensive practical report of this scope and the current cost of such reviews, and because it would limit the responsiveness of the GINA Strategy Report to emerging evidence and new developments in asthma management. However, the Science Committee reviews relevant systematic reviews conducted with GRADE methodology as part of its normal review process, once such reviews are published. GINA recommendations are constantly being reviewed and considered for update as new evidence (including GRADE-based systematic reviews on specific topics) is identified and indicates the need.

Literature screening and review

Articles are first pre-screened by the Editorial Assistant to remove duplicates, articles already reviewed, animal studies, protocols, pilot studies, non-English articles, and non-asthma articles. Each remaining article identified by the literature search is screened in Covidence for relevance and major quality issues by at least two non-conflicted members of the Science Committee. The full text of each article selected during screening is then reviewed for quality and relevance by at least two members of the Committee, neither of whom may be an author or have any other declared conflict of interest in relation to the article. Articles that have been accepted for publication and are published online in advance of print are eligible for full-text review if the approved/corrected copy-edited proof is available. All Committee members receive a copy of all abstracts and full-text articles, and non-conflicted members have the opportunity to provide comments during the pre-meeting review period. The members evaluate the full-text article, and answer written questions in a review template about whether the scientific data impact on GINA recommendations, and if so, what specific changes should be made. In 2020, questions based on the Critical Appraisal Skills Programme (CASP) checklist[2] were provided in the review template (Table 2) to assist in evaluation of systematic reviews.

[2] Critical Appraisal Skills Programme. CASP Checklist: 10 questions to help you make sense of a systematic review: CASP; 2018. Available from: https://casp-uk.net/images/checklist/documents/CASP-Systematic-Review-Checklist/CASP-Systematic-Review-Checklist_2018.pdf.

Table 2. Structured assessment of articles identified for review during screening phase

A. All articles	Based on this article, are any changes needed to the GINA report? (YES/NO)
	If **NO**, state the reason(s): Not relevant Methodology (state problem) Already well covered in GINA Strategy Report Other (state)
	If **YES**, identify the PICOT question addressed by the study: P (population) I (intervention) C (comparator) O (main outcomes) T (time)
B. Systematic reviews rated YES at part A	1. Was there a clearly focused question? (YES/NO)
	2. Did the authors look for the right type of papers? (YES/NO)
	3. Were all important, relevant studies included? (YES/NO)
	4. Was enough done to assess quality? (YES/NO)
	5. If results combined, was this reasonable? (YES/NO)
	6. What are the overall results? (Summarize)
	7. How precise are the results? (Describe)
	8. Can results be applied to other populations? (YES/NO)
	9. Were all important outcomes considered? (YES/NO)
	10. Are benefits worth the harms and costs? (YES/NO)
C. All articles rated YES at part A	Should any of the recommendations/statements/evidence levels in the current GINA Strategy Report be changed? (YES/NO) If YES, provide draft revised text for discussion.
	Should the article be added to the GINA Strategy Report reference list? (YES/NO) If YES: Where should it be added? Should it replace an existing reference?
	Should a new section on this topic be added to the GINA Strategy Report? (YES/NO) If YES, provide draft text for discussion.

Discussion and decisions during Science Committee meetings

Each article that is assessed, by at least one reviewer, to potentially impact on the GINA Strategy Report is discussed in a Science Committee meeting (virtual or face-to-face). This process comprises three parts, as follows:

1. Quality and relevance of original research and systematic review articles. First, the Science Committee considers the relevance of the article to the GINA Strategy Report, the quality of the study, the reliability of the findings, and the interpretation of the results, based on the responses from reviewers and discussion by members of the Committee. For systematic reviews, GRADE assessments, if available, are taken into account. However, for any systematic review, Committee members also independently consider the clinical relevance of the question addressed by the review, and the scientific and clinical validity of the included populations and study design. During this discussion a Committee member who is an author, or who declares any other conflict of interest relating to the study, may be requested to provide clarification or respond to questions about the study, but they may not otherwise take part in this discussion about the quality and relevance of the article.

2. Decision about inclusion of the evidence. During this phase, the Science Committee decides whether the article or its findings affect GINA recommendations or statements and should be included in the GINA Strategy Report. These decisions to modify the report or its references are made by consensus by Committee members present, or by vote if needed. Again, any member with a conflict of interest is excluded from these decisions. If the Chair is an author of an article being reviewed, or has a conflict of interest related to the article, an alternative acting Chair is appointed to lead the discussion in part 1 and the decision in part 2 for that article.

3. Discussion about related changes to the GINA Strategy Report. If the Science Committee resolves to cite the article or its findings in the report, a Committee member who is an author or conflicted member is permitted to take part in subsequent deliberations. These include discussions about and decisions on changes to the report, including the positioning of the study findings in the report and the way that they would be integrated with existing (or other new) components of the GINA management strategy. These discussions may take place immediately, or over the course of the year as new evidence emerges or as other changes to the report are agreed and implemented.

The approach to managing conflicts of interest, as described above, also applies to members of the GINA Board who *ex-officio* attend GINA Science Committee meetings.

As with all previous GINA Strategy Reports, levels of evidence are assigned to management recommendations where appropriate. Current criteria (Table 3) are based on those originally developed by the National Heart Lung and Blood Institute. From 2019, GINA has included in 'Level A' strong observational evidence that provides a consistent pattern of findings in the population for which the recommendation is made, and has also described the values and preferences that were taken into account in making major new recommendations. The table was updated in 2021 to avoid ambiguity about the positioning of observational data and systematic reviews.

Table 3. Description of levels of evidence used in the GINA Strategy Report

Evidence level	Sources of evidence	Definition
A	Randomized controlled trials (RCTs), systematic reviews, observational evidence. Rich body of data	Evidence is from endpoints of well-designed RCTs, systematic reviews of relevant studies or observational studies that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	Randomized controlled trials and systematic reviews. Limited body of data	Evidence is from endpoints of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs or systematic reviews of such RCTs. In general, Category B applies when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials or observational studies	Evidence is from non-randomized trials or observational studies.
D	Panel consensus judgment	This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above listed criteria.

New therapies and indications

The Strategy Report is a global strategy document. Since regulatory approvals differ from country to country, and manufacturers do not necessarily make regulatory submissions in all countries, some GINA recommendations are likely to be off-label in some countries. This is a particular issue for pediatrics, where across different diseases, many treatment recommendations for pre-school children and for children aged 6–11 years are off-label.

For new therapies, GINA's aim is to provide clinicians with evidence-based guidance about new therapies and their positioning in the overall asthma treatment strategy as soon as possible; otherwise the gap between regulatory approval and the periodic update of many national guidelines is filled only by advertising or educational material produced by the manufacturer or distributor. For new therapies for which the GINA Science Committee considers there is sufficient good-quality evidence for safety and efficacy or effectiveness in relevant asthma populations, recommendations may be held until after approval for asthma by at least one major regulatory agency (e.g. European Medicines Agency or US Food and Drug Administration), since regulators often receive substantially more safety and/or efficacy data on new medications than are available to GINA through peer-reviewed literature. However, decisions by GINA to make or not make a recommendation about any therapy, or about its use in any specific population, are based on the best available peer-reviewed evidence and not on labeling directives from regulators.

For existing therapies with evidence for new regimens or in different populations, the Science Committee may, where relevant, make recommendations that are not necessarily covered by regulatory indications in any country at the time, provided the Committee is satisfied with the available evidence around safety and

efficacy/effectiveness. Since the GINA Strategy Report represents a global strategy, the report does not refer to recommendations being 'off-label'. However, readers are advised that, when assessing and treating patients, they should use their own professional judgment and should also take into account local and national guidelines and eligibility criteria, as well as locally licensed drug doses.

External review

Prior to publication each year, the GINA Strategy Report undergoes extensive external review by patient advocates and by asthma care experts from primary and specialist care in multiple countries. There is also continuous external review throughout the year in the form of feedback from end-users and stakeholders through the contact form on the GINA website.

LITERATURE REVIEWED FOR GINA 2023 UPDATE

The GINA Strategy Report has been updated in 2023 following the routine twice-yearly review of the literature by the GINA Science Committee. The literature searches for 'clinical trial' publication types (see above), systematic reviews and guidelines identified a total of 3698 articles, of which 3118 duplicates/animal studies/non-asthma/pilot studies and protocols were removed. A total of 580 articles underwent screening of title and abstract by at least two reviewers, and 491 were screened out for relevance and/or quality. A total of 89 articles underwent full-text review by at least two members of the Committee, and 52 articles were subsequently discussed at meetings of the Committee.

The Strategy Report contains a list of key changes in GINA 2023, and a tracked changes copy is archived on the GINA website at www.ginasthma.org/archived-reports.