METHODOLOGY USED BY THE GINA SCIENCE COMMITTEE FOR THE 2019 REPORT

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, and to provide yearly updates to these documents. The members are recognized leaders in asthma research and clinical practice with the 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 as well as from diverse geographic regions. The Science Committee meets twice yearly in conjunction with the American Thoracic Society (ATS) and European Respiratory Society (ERS) international conferences, to review asthma-related scientific literature. Statements of interest for Committee members are found on the GINA website www.ginasthma.org.

THE GINA STRATEGY REPORT

The Global Strategy for Asthma Management and Prevention provides a comprehensive and integrated approach to asthma management that can be adapted for local conditions and for individual patients. It focuses not only on the existing strong evidence base, but also on clarity of language and on providing tools for feasible implementation in clinical practice. The report is updated each year.

The GINA report is not a guideline, but an integrated evidence-based strategy focusing on translation into clinical practice. Recommendations are framed, not as answers to isolated PICOT questions (i.e. questions formulated in terms of the Population, Intervention, Control group, Outcome measure and Time period of interest), but as part of an integrated strategy, in relation to:

- The GINA goals of preventing asthma deaths and exacerbations, and improving symptom control
- Current understanding of underlying disease processes
- Human behavior (of health professionals and patients/carers)
- Implementation in clinical practice
- Global variation in populations, health systems and medication access

PROCESSES FOR UPDATES AND REVISIONS OF THE GINA REPORT

GINA processes for the review of evidence and development of recommendations for GINA reports, including handling of conflict of interest, were reviewed by the Science Committee and approved by the Board in September 2018, and are described below.

Literature search

For each meeting of the GINA Science Committee, a rolling PubMed search is performed covering approximately 18 months, using two search strategies established by the Committee, namely: 1) asthma, all fields, all ages, only items with abstracts, clinical trial, human; and 2) asthma and meta-analysis, all fields, all ages, only items with abstracts, human. The ‘clinical trial’ publication type includes not only conventional randomized controlled trials, but also pragmatic trials and observational studies. Phase I and Phase II studies are excluded from routine initial review, but adequately-sized Phase II studies may be reviewed later, if a corresponding Phase III study is considered for inclusion. The respiratory community is also invited to submit to the Program Director any other peer-reviewed publications that they believe should be considered, providing an abstract and the full paper are 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.

Screening and review

Articles identified by the cumulative search of the literature, after removal of those already reviewed, are pre-screened for relevance by the Editorial Assistant (a medical librarian) and members of the Science Committee. Each publication selected from pre-screening is allocated to be reviewed for relevance, quality and implications for the GINA strategy by at least two members of the Science Committee, neither of whom may be an author or co-author nor declare a conflict of interest in relation to the publication. All Science Committee and Board members receive a copy of all of the abstracts and non-conflicted members have the opportunity to provide comments during the pre-meeting review period. Members evaluate the abstract and the full publication, and answer written questions about whether the scientific data impact on GINA recommendations and, if so, what specific changes should be made. A list of all publications reviewed by the Committee is posted on the GINA website, www.ginasthma.org.

Discussion and decisions during Science Committee meetings

Each publication that was considered by at least one of the reviewers to potentially impact on the GINA Report is discussed in a face to face Science Committee meeting. This process comprises three parts:

- evaluation of the quality and relevance of the evidence
- a decision about inclusion of the evidence in the Report
- (if included) discussion about related changes to the Report.

First, the Committee considers the quality of the study, the reliability of the findings, the interpretation of the results, and the relevance of the study to the GINA Report, based on the responses from reviewers and discussion among members of the Committee. During this discussion, an author may be requested to provide clarification or respond to questions relating to the study, but they may not otherwise take part in the discussion about the publication. They may also not participate in the second phase, during which the Committee decides whether the publication or its findings should be included in the GINA Report. These decisions to modify the report or its references are made by consensus by Committee members present. If the Chair is an author on a publication being reviewed, an alternative Chair is appointed to lead the discussion in part 1 and the decision in part 2 for that publication. If the Committee resolves to include the publication in the Report, an author is permitted to take part in the third phase that involves 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 time as new evidence emerges or as other changes to the Report are agreed and implemented. The above conflict of interests considerations also apply to members of the GINA Board who ex-officio attend GINA Science Committee meetings.

In 2009, after carrying out two sample reviews using the GRADE system, GINA decided not to adopt this methodology for its general processes because of the major resource challenges that it would present. This decision also reflected that, 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; and the GINA Report is not constructed as a series of individual 'PICOT' questions, but as an integrated strategy. As with all previous GINA reports, levels of evidence are assigned to management recommendations where appropriate. A description of the current criteria is found in Table A, which was developed by the National Heart Lung and Blood Institute. From 2019, GINA is also describing the values and preferences that contributed to major new recommendations.

New therapies and indications

For new therapies, the Committee makes recommendations after approval for asthma by at least one major regulatory agency, but decisions are based on the best available peer-reviewed evidence and not on labeling directives from government regulators. The rationale for waiting for an indication by a major regulatory agency (i.e. European Medicines Agency or Food and Drug Administration) is first, as a safety check, since the major

regulators are provided with a much more substantial dossier of evidence than may be available to GINA in the peer-reviewed literature; and second, so that a new medication is not included in GINA recommendations until it can be prescribed by many clinicians.

In May 2018, in the context of discussion about new evidence for use of long-term low dose macrolides to reduce exacerbations in moderate-severe asthma, the GINA Science Committee and Board agreed that the Committee may, where relevant, consider making off-label recommendations for existing therapies, provided the Committee is satisfied with the available evidence around safety and efficacy or effectiveness.

Table. Description of levels of evidence used in the 2019 GINA report

Evidence level	Sources of evidence	Definition
A	Randomized controlled trials (RCTs) or meta-analyses. Rich body of evidence.	Evidence is from endpoints of well-designed RCTs or meta-analyses of relevant 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	RCTs and meta-analyses. Limited body of evidence.	Evidence is from endpoints of intervention studies that include only a limited number of patients, post-hoc or subgroup analysis of RCTs or meta-analysis of such RCTs. In general, Category B pertains 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. Evidence may be supported by good quality observational studies.
C	Only non-randomized trials or observational studies.	Evidence is only from outcomes of uncontrolled or 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.

This table was developed by the National Heart Lung and Blood Institute. It has been used by GINA since 2002. In 2014, it was modified by addition of meta-analyses to the data that may contribute to Level A evidence.