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Adherence stages measured by patient-reported outcome instruments in adults with asthma: a scoping review

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ABSTRACT

Objective: Individuals who are adherent to their asthma inhaled maintenance medication: (1) initiate their treatment (take the first dose); (2) implement it (take it as per prescribed dosing regimen); and persist with it (take it for the entire prescribing period). To avoid unnecessary hospitalizations and costs, patient adherence should be routinely assessed. To this end, we aimed to identify patient-reported outcome instruments (PROs) used for measurement of patient adherence to inhaled maintenance medication in asthmatic adults and to report on the adherence stage that these instruments measured. **Data sources:** We conducted a scoping review of six databases. **Study selection:** We searched for studies in which PROs were used to measure patient adherence to inhaled maintenance medication in asthmatic participants aged ≥ 18 years. We extracted and synthesized data in order to list the available PROs and to report the adherence stages that these instruments measured. **Results:** We included 186 studies (87 PROs). Among all 87 instruments, none were found to measure all three adherence stages. We found that 1 measured initiation, 2 evaluated initiation and implementation, 74 assessed implementation, 7 measured implementation and persistence. The most used instrument ($n = 41$ studies or 22%) was the *Self-Reported Medication-Taking Scale*, which was found to assess implementation only. **Conclusion:** Our results suggest that no single PRO exists to measure initiation, implementation and persistence with asthma inhaled maintenance medication. Results from this review could therefore guide the development or refinement of PROs that would aim to measure all three adherence stages.

Abbreviations: COSMIN: Consensus-based Standards for the selection of health Measurement Instruments; EMD: Electronic monitoring device; GINA: Global Initiative for Asthma; ICS: Inhaled corticosteroids; IAS: *Inhaler Adherence Scale*; LABA: Long-acting β_2 -agonists; MARS: *Medication Adherence Report Scale*; MARS-A-10: *Medication Adherence Report Scale for Asthma*; MMAS-8: Morisky Medication Adherence Scale, 8 items; PRO: Patient-reported outcome; SRMTS: *Self-Reported Medication-Taking Scale*

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Introduction

Asthma, a chronic but treatable respiratory disease, negatively affects millions of people worldwide, with a global incidence of 75 million, a prevalence of 339 million, and years lived with disability of 13 million in 2016 [1].

To reduce risks of future exacerbations and optimize asthma control, the *Global Initiative for Asthma (GINA) Committee* has proposed a stepwise pharmacological approach and suggested clinicians to increase

the prescribed dose of inhaled corticosteroids (ICS) in individuals with uncontrolled asthma, but who are adherent to their inhaled maintenance treatment [2]. Nevertheless, patients who require the highest doses of ICS to prevent asthma from becoming uncontrolled are also characterized by high health resource utilization and, in turn, impose a costly burden on health systems [3]. Although the prescribed dose of ICS should only be increased in patients who are adherent to their treatment, a large proportion (>80%) of these

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patients have been shown not to fully adhere to their treatment [4]. In addition and regardless of the disease severity, patients have been shown to underuse their prescribed medication [5–8], which, in turn, has led to poor symptom control [5,7], increased health resource utilization [5,8], rising costs [5,7] and asthma mortality [9]. In this context, considerable efforts have been made to develop and evaluate interventions aiming to enhance adherence in patients, and the GINA Committee has stressed the importance of measuring patient adherence in routine care [2].

Patient adherence to medications has long been defined as the extent to which patients take their medications as recommended by their health care provider [10] and described by ambiguous terms that make it difficult to quantify [11]. Based on the results of a systematic literature review on conceptual approaches to adherence research, as well as on subsequent discussions between international experts and on behavioral and pharmacological sciences, Vrijens et al. (2012) have attempted to unify the terminology used to describe adherence. With the overarching goal of helping the conduct, analysis, and interpretation of adherence-related research, they proposed the *Ascertaining Barriers to Compliance (ABC) Taxonomy for Medication Adherence* [11,12], which conceptualizes patient adherence using three quantifiable parameters:

1. *Initiation*: “when the patient takes the first dose of a prescribed medication” [11,12];
2. *Implementation*: “the extent to which the patient’s actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken” [11,12];
3. *Persistence*: “the time elapsed from initiation until eventual treatment discontinuation,” that is: “when the next dose is omitted and no more doses are taken thereafter” [11,12].

According to the *ABC Taxonomy for Medication Adherence* [11,12], only patients who *initiate*, *implement* and *persist* with their treatment could be described as *adherent*.

In asthma and as reported above, patient adherence to pharmacological treatment has consistently been reported to be poor [13–15]. In a population of 69,652 asthmatic subjects prescribed ICS, alone or in combination with a long-acting β_2 -agonist (LABA), for the first time, about 14%–18% did not *initiate* asthma inhaled maintenance treatment within 30 days [16]. In addition, *implementation* of ICS/ICS-LABA

was poor in this population, with only 3%–7% who was found to implement the dosing regimen as prescribed by their clinician. At six months, *persistence* with ICS or ICS-LABA combination was as low as 60%–64% [16], and over a 12-month period, another study reported that 0%–22% of individuals aged ≥ 12 years and diagnosed with asthma have persisted with their inhaled maintenance treatment [17].

To measure patient implementation and persistence with asthma treatment, electronic monitoring devices (EMDs) might be considered as goal standard measures [12]. Recent advances in e-health research have showed that EMDs may be more than measurement instruments, as they can also be conceptualized as successful self-management intervention components to improve patient adherence across diseases, including asthma [18].

Although subjective measurements, patient-reported outcome instruments (PROs), including questionnaires and health diaries, also serve to measure patient adherence to treatment. Even though clinicians’ decisions to initiate of high-cost precision therapy in severe asthma patients may require objective measurements of patient adherence to ICS [19], PROs have been widely used to measure patient adherence to asthma treatments in individuals with mild-to-moderate asthma, in both clinical and research settings [5,20–22], because they are easy to implement [12].

The choice of any PRO instrument should depend on its reliability (whether adherence scores for patients who have not changed are the same [23]), validity (the degree to which adherence scores reflect the concept of adherence [23]), responsiveness (the ability of a PRO to detect change over time in adherence [23]) and interpretability (e.g. minimal clinically important change). In adults with asthma, some PROs have been validated for adherence measurement, including the *Medication Adherence Report Scale for Asthma* (MARS-A-10) [24,25] and, in the past few years, the *Medication Adherence Reasons Scale* (MAR-Scale) [26], *Medication Intake Survey-Asthma* (MIS-A) [27] and the *Test of the Adherence to Inhalers* (TAI) [28]. We hypothesize that several additional PROs are used to measure adherence and it remains unknown whether any PROs, which are reported to measure patient adherence, actually measure initiation of, implementation of and persistence with inhaled asthma maintenance treatment. In this context, we aimed to identify all PROs used for assessment of adherence to inhaled maintenance medications in adults with asthma and to report on the adherence stages (initiation, implementation and persistence) that these instruments targeted. As a result, we hope to generate a list of items that could be used to refine

the existing instruments and subsequently enable simple, timely and inexpensive measurement of initiation of, implementation of and persistence with ICS/ICS-LABA in research and clinical settings.

Methods

Search methods for identification of studies

We conducted a scoping review [29] and sought for any PROs that were reported but not restricted to be used for measurement of patient adherence to inhaled maintenance medication among adults with asthma.

We searched CINAHL, the COCHRANE Library, EMBASE, MEDLINE, PsycINFO and Web of Science, from inception to December 2013. Searches were updated up to August 27, 2018 later. With the assistance of an experienced librarian (Scientific Library, Laval University, Quebec City, Quebec, Canada) and based on the Cochrane Handbook [30], we designed two search strategies, one that denoted adherence and the other asthma. Both search strategies were based on text and thesaurus words. They were enriched by synonyms, related terms, variant spellings and truncated words. We used the syntax that was specific to each database. No restrictions in regards to language or publication dates were applied. Today, detailed search strategies are still available elsewhere (see Gagne et al. (2018) [31]).

Selection of studies

We exported our search results to Thomson Reuters® ENDNOTE®. One reviewer (MG) identified and eliminated duplicates. To identify potentially relevant studies, two reviewers (MG, NP) independently read titles and abstracts (titles and abstracts: $n = 6,064$; agreement: 94%; Cohen's κ : 0.95). Reviewers' disagreements were resolved by consensus later. When searches were updated, one reviewer (MG) identified relevant studies. Based on the full-text articles, the two reviewers identified the eligible reports (full-text articles: $n = 654$; agreement: 79%; Cohen's κ : 0.84). Later on, reviewers' disagreements were resolved by consensus. When we updated our searches, only one reviewer (MG) was responsible for identifying the eligible reports.

Articles that fulfilled the following criteria were included:

1. Instrument of interest: any PRO;
2. Construct of interest (including, but not restricted to): adherence to asthma inhaled maintenance medication;
3. Population of interest (including, but not restricted to): adults with asthma.

We included articles that were written in English, French or Spanish (both MG and NP were able to read these languages). Articles that did not present the items of their PRO in the text, in another publication cited in reference, or in any online supporting information were excluded. We excluded articles in which PROs were solely used to measure medication use (e.g. prescribed dosing regimen) or elicit barriers to and beliefs associated with adherence. We excluded abstracts, authors' replies, clinical practice guidelines, commentaries, congresses, editorials, letters to the editor, narrative or systematic reviews and meta-analysis.

Data extraction and management

For each PRO, two reviewers (MG, NP) independently extracted the following characteristics (please refer to Table 1 for definitions):

1. Type of instrument;
2. Mode of administration;
3. Number of items;
4. Specific items;
5. Reference period;
6. Type of question;
7. Response options;
8. Overall score calculation and interpretation.

The data extraction form is available as [supplementary material \(Supporting Information Table S1\)](#).

Reviewers' disagreements were resolved either by consensus or discussion with a third author (JM). Again, when searches were updated, only one reviewer (MG) extracted data.

Data analysis and synthesis

The data on PRO characteristics were summarized descriptively. Based on the *ABC Taxonomy for Medication Adherence* [11,12], we determined the adherence stage(s) that each item measured. Then, we listed the PROs according to the adherence stage(s) that they were found to evaluate, and summarized the results descriptively.

Results

Study selection

Figure 1 illustrates the flow of information through the different phases of our scoping review. Our electronic searches resulted in 7811 unique records. Of those, 879 were retrieved for full-text screening.

Table 1. PRO characteristics: definitions and attributes.

Characteristics	Definition/attribute
Type of PRO	Questionnaire Health diary
Mode of administration	Self-administered Interviewer-administered (either face-to-face or telephone) Computer-administered
Type of question	
Open-ended	"Questions to which no answers are provided by the investigator" ^a
Closed-ended	"Questions for which the range of possible answers is specified by the investigator and the respondent is asked to make a choice from among the answer provided" ^a
Response options	
Event log	"Specific events are recorded as they occur using a patient diary or other reporting system (e.g. interactive voice response system)" ^b
Checklist	"Checklists provide a simple choice between a limited set of options, such as True, False, and Don't know. Some checklists ask patients to place a mark in a space if the statement in the item is true." ^b
Continuous—VAS	"A line of fixed length (usually 100 mm) with words that anchor the scale at the extreme ends and NO words describing the intermediate positions. Patient are instructed to place a mark on the line corresponding to their perceived state." ^b
Continuous—Anchored or categorized VAS	"A VAS that has the addition of one or more intermediate marks positioned along the line with reference terms assigned to each mark to help patients identify the locations (e.g. half-way) between the ends of the scale." ^b
Continuous—Likert scale	"An ordered set of discrete terms and statements from which the patients are asked to choose the response that best describes their state or experience." ^b
Rating scale	"A set of numerical categories from which patients are asked to choose the category that best describes their state or experience. The ends of rating scales are anchored with words, but the categories do not have labels." ^b

PRO: patient-reported outcome instrument; VAS: visual analog scale.

^aQuoted from White *et al.* (2008) [42].

^bQuoted from US Department of Health Human Services FDA Center for Drug Evaluation Research *et al.* (2006) [43].

Finally, 186 studies (197 citations) met our inclusion criteria, and 87 PROs were identified.

PROs used for measurement of adherence to inhaled maintenance medication in adults with asthma

The characteristics of the 87 PROs (>95% being questionnaires) are summarized in Table 2. About half of the PROs did not refer to a specific (or prescribing) period when participants were asked about their adherence behavior.

Figure 2 illustrates the percentage of PROs that were found to measure each adherence stage. Based on the *ABC Taxonomy* [11,12], we found that none of the 87 included PROs measured all three adherence stages (initiation, implementation and persistence). One *ad hoc* questionnaire measured initiation. Two *ad hoc* questionnaires evaluated both initiation and implementation. Seventy-four PROs assessed implementation of the prescribed regimen. Seven PROs measured implementation and persistence. Finally, three instruments were used to assess adherence, but were not found to measure any of the three adherence stages. These questionnaires evaluated barriers to adherence, beliefs about medication or medication use (e.g. prescribed dosing regimen).

Out of the 87 PROs, 68 were only used once. The most used instrument ($n = 41$ studies, or 22%) was the *Self-Reported Medication-Taking Scale* (SRMTS, also referred to as the 4-item *Morisky Medication Adherence Scale* by several authors) [32]. Twenty-nine

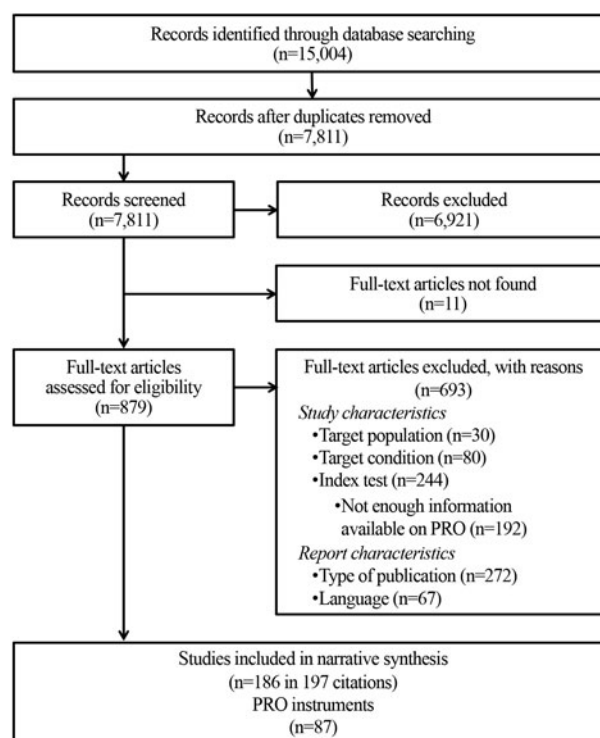


Figure 1. Flow of information throughout the review. Based on the PRISMA statement [41].

other studies (16%) used a PRO that was adapted from the SRMTS, including the *Inhaler Adherence Scale* (IAS) [33,34] ($n = 8$ studies, or 4%). The 9-item *Medication Adherence Report Scale* (MARS-9) [35], including the MARS for Asthma (MARS-A-10) [24,25], the MARS-5 [36] and the MARS-4 [35], was the second most used instrument ($n = 34$ studies, or

18%). The third most used PRO ($n=24$ studies, or 13%) was the 8-item *Morisky Medication Adherence Scale* (MMAS-8). The SRMTS, the IAS, the MARS-A-10 and the MMAS-8 were found to measure implementation of asthma inhaled maintenance medication.

Supporting Information Table S2 presents the 87 PROs that were used at least once for the measurement of adherence to inhaled maintenance medication in adults with asthma. PROs are listed according to the adherence stage(s) that they were found to assess, based on the *ABC Taxonomy for Medication Adherence* [11,12]. For each instrument, we show the number of items, the types of questions, the types of response options and the number of studies that used the instrument. Based on our team's previous work [31], we additionally provide information on the measurement properties of the few PROs that have been validated in adults with asthma ($n=13/87$).

Discussion

Summary of findings

Patient adherence to asthma inhaled maintenance medication is crucial to avoid uncontrolled asthma [5,7], increased health resource utilization [5,8] and rising costs [5,7]. As per the *ABC Taxonomy for Medication Adherence* [11,12], patients who adhere to their prescribed treatment are those who *initiate*, *implement* and *persist* with it [11,12]. In this scoping review, we identified 87 PROs that were used for assessment of patient adherence to inhaled maintenance medication in adults with asthma. Our results showed that most of these PROs allowed to measure implementation of asthma medications, which lead us to make four observations.

First, our results highlighted that almost all the PROs used for measurement of adherence to inhaled maintenance medication in adults with asthma exclusively focused on the measurement of implementation, even though patient adherence has been described as a three-stage process [11,12]. Our results are consistent with those drawn from two systematic reviews. Particularly and also based on the *ABC Taxonomy* [11], Dima et al. (2015) reported that the majority of studies on determinants of asthma inhaler use focused on implementation of ICS [37]. Similarly and also based on the *ABC Taxonomy*, Nguyen et al. (2014) showed that the majority of self-report adherence scales measured implementation of the prescribed treatment in individuals diagnosed with various diseases [38].

Table 2. Characteristics of the PROs ($N=87$).

Characteristics ^a	PRO, n (%)
Type of instrument	
Questionnaire	84 (96%)
Diary	3 (4%)
Mode of administration ^b	
Self-administered	45 (52%)
Interviewer-administered, face-to-face	26 (30%)
Interviewer-administered, telephone	10 (11%)
Computer-administered	7 (8%)
Unclear mode of administration	4 (5%)
Type of question	
Only opened-ended	13 (15%)
Only closed-ended	64 (74%)
Both opened-ended and closed-ended	9 (10%)
Unclear	1 (1%)
Response options	
Event log	3 (3%)
Checklist	42 (48%)
Visual analog scale	2 (2%)
Likert scale	21 (24%)
Rating scale	1 (1%)
Both checklist and Likert scale	3 (3%)
Both checklist and rating scale	1 (1%)
N/A: open-ended	13 (15%)
Unclear response options	1 (1%)
Reference period	
Last week	11 (13%)
Last month	3 (3%)
Last three months	5 (6%)
Last year	5 (6%)
Other	18 (21%)
Unspecified	42 (48%)
Both specified and unspecified	3 (3%)

PRO: patient-reported outcome instrument; VAS: visual analog scale.

^aDefinitions of PROs' characteristics are presented in Table 1.

^bPercentages exceed 100%, because there was sometimes more than one mode of administration per PRO.

Second, in this scoping review, many of the PROs that were found to measure persistence or implementation did not precisely define the reference or prescribing period (e.g. in the last month). Nonetheless, Vrijens et al. (2016) have underlined the importance of referring to a specific prescribing period when assessing persistence with asthma treatments, but also implementation of ICS [12]. In patients with HIV [human immunodeficiency virus], authors found that PROs, compared with EMDs, were more accurate when they referred to a 1-month period rather than a 3- and 7-day period [39]. In asthma, further studies are needed to determine the most appropriate reference period.

Third, not surprisingly, the oldest questionnaire—the SRMTS [32]—was the most used PRO for measurement of adherence to inhaled maintenance medication in adults with asthma. Given that the SRMTS has been developed and validated within a population of hypertensive patients [32], we suggest that clinicians assess implementation of asthma maintenance treatment using an instrument that would have been previously validated within a population of individuals with asthma. To the best of our knowledge, 13 PROs have previously been

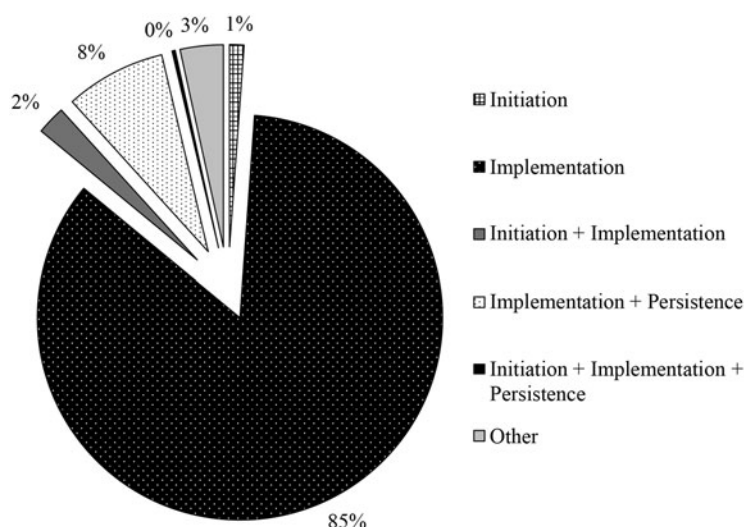


Figure 2. Adherence stages. None of the 87 included PROs were found to measure initiation, implementation, and persistence with asthma inhaled maintenance medication. We found that 1 PRO measured initiation, 2 evaluated initiation and implementation, 74 assessed implementation, 7 measured implementation and persistence and 3 did not measure any of the three adherence stages.

validated among adults with asthma and, in a recent systematic review of measurement properties, our team showed that there was a combination of positive, negative and unknown evidence in regards to the reliability and validity of the PROs that were validated to assess patient adherence to asthma medication in adults with asthma [31]. Although PROs tend to overestimate patient adherence (when compared with EMDs), it remains that to decide on the most appropriate instrument that could be used to measure implementation of inhaled maintenance medication in adults with asthma, further high-quality studies, conducted in accordance with the published COSMIN-based Standards for the selection of health Measurement INstruments (COSMIN) are needed, as we previously reported [31]. Based on a Delphi survey of 43 epidemiology, statistics, psychology and clinical medicine experts, the COSMIN group has reached international consensus on the definitions of domains of measurement properties for PROs [23]. Accordingly, we expect researchers to evaluate the reliability (whether adherence scores for patients who have not changed are the same [23]), validity (the degree to which adherence scores reflect the concept of adherence [23]), responsiveness (the ability of a PRO to detect change over time in adherence [23]) and interpretability (e.g. minimal clinically important change) of the available PROs, following guidance provided by the COSMIN.

Finally, results from our scoping review can serve the refinement of the existing PROs, as they can be used to generate a list of items allowing to assess each adherence stage. Proper measurement of

initiation of, implementation of and persistence with asthma treatment is crucial in both clinical and research settings. It needs to consider both the adherence stages [11,12] and the measurement properties of the available PROs [23]. Because no specific PRO can be recommended for adherence measurement use at this point (mainly due to study poor methodological quality) [31] and because PROs need to evaluate initiation of and persistence with treatment, in addition to implementation, we believe that measurement of adherence to asthma inhaled maintenance medication could be improved by assessing, in an empathic manner and specifying the prescribing period: (1) whether patients *initiated* their treatment; (2) in those who initiated it, whether they were *persistent* with it; and (3) in those who were persistent, whether they *implemented* it.

Strengths and limitations

Our systematic scoping review carries important messages, due to the fact that it lists several PROs that exist to measure each adherence stage, as defined by the *ABC Taxonomy for Medication Adherence* [11,12]. We are confident that our electronic searches, designed to optimize their sensitivity and lower their specificity [30], identified an important and a representative number of PROs that were reported to be used for assessment of adherence to inhaled maintenance medication in adults with asthma.

Despite these strengths, our scoping review has some limitations. First, due to the high number of

PROs included in this review, we chose not to include articles that reported measuring adherence to inhaled maintenance medication, but that did not explicitly state the items of the PRO within the text or a reference. Even though it would have been interesting to list these instruments, we still believe that we succeeded in identifying a large and a representative number of PROs. Second, in the present scoping review, we neither assessed the quality of the included studies, nor the quality of the included PROs. The reason for this is that our aim was to identify the adherence stages targeted by the available PROs in order to generate a list of items to measure initiation, implementation, and persistence, not to aggregate estimates of measurement properties, or pool adherence rates. Further studies, based on factorial analyses and item response theory, are needed to assess whether these items belong, from a statistical point of view, to these adherence stage [40].

Conclusion

Although several different PROs have been used to measure adherence to inhaled maintenance medication in adults with asthma, our results suggest that none actually target all three adherence stages: initiation, implementation and persistence. Our scoping review therefore highlights the need to adapt or develop, and further validate PROs that could be used to measure initiation of, persistence with, and implementation of asthma inhaled maintenance medication.

To determine the most appropriate PRO for measurement of the three adherence stages, further high-quality studies that would aim to evaluate the measurement properties of these instruments are needed. As a result, proper assessment of each adherence stage could help clinicians to understand patients' behaviors better, and researchers to better assess the impact of interventions designed to optimize adherence to beneficial treatments, like the use of inhaled maintenance medication in adults with asthma.

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Author contributions

Substantial contributions to the conception or design of the work; or the acquisition of the work; or the analysis, or interpretation of data for the work: MG, LPB, NP, JM

Drafting the work: MG

Revising the work critically for important intellectual content: LPB, NP, JM

Final approval of the version to be published: MG, LPB, NP, JM

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: MG, LPB, NP, JM

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