Original Article

Results from a UK consensus about the optimal prescribing of medium strength triple therapy in uncontrolled adult asthma patients in the NHS

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Abstract

Context: An inhaled corticosteroid (ICS) in combination with a long-acting β2-agonist (LABA) is a common treatment approach for asthma patients not controlled on ICS alone, but a significant proportion of patients remain uncontrolled on this combination and treatment adherence can also be a challenge. One of the options for adults whose asthma is uncontrolled in an ICS/LABA is the addition of a long-acting muscarinic receptor antagonist (LAMA), an approach commonly referred to as 'triple therapy'. The use of medium-strength ICS/LABA/LAMA is established in treating chronic obstructive pulmonary disease but is less well-established in asthma. Lack of clarity exists regarding who should prescribe ICS/LABA/LAMA and in which patients, and this is compounded by a lack of consistency among guidelines. **Aims:** To define the optimal prescribing of medium-strength ICS/LABA/LAMA triple therapy in adult asthma patients uncontrolled on ICS/LABA. **Methods and Material:** Using a modified Delphi method, a panel of experts developed 39 *Likert* scale statements across six key domains. These statements were used to develop an online survey that was distributed to healthcare providers (HCPs) working with adult asthma throughout the UK. The threshold for consensus was set at 75%. **Results:** In total, 314 responses were received from primary and secondary care stakeholders involved in the management of asthma. On analysis, 22/39 statements reached a very strong agreement (≥90%) and 16/39 attained strong agreement (≥75% and < 90). From these results, the panellists developed a set of twelve recommendations to help define how an optimal approach for prescribing triple therapy in patients who are uncontrolled on an ICS/LABA can be achieved. **Conclusions:** The strength of agreement shows that HCPs support the use of medium-strength ICS/LABA/LAMA triple therapy in appropriate asthma patients, and that clarity is needed regarding how best this can be achieved. The proposed set of recommendations provides such guidance to support the prescribing of triple therapy in primary care.

Keywords: Asthma, general practice, hospital referral, respiratory medicine, United Kingdom

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Received: 20-06-2024 **Revised:** 04-09-2024
Accepted: 17-09-2024 **Published:** 09-12-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1082_24

Introduction

There is currently no cure for asthma, so the goal of treatment is to achieve good symptom control, and to minimise future risk of asthma-related mortality, exacerbations, persistent airflow limitation and the side-effects of treatment.[1,2] Uncontrolled

How to cite this article: Russell RE, Attar-Zadeh D, Harper N, Mosgrove F, Rush L, Singh D. Results from a UK consensus about the optimal prescribing of medium strength triple therapy in uncontrolled adult asthma patients in the NHS. J Family Med Prim Care 2024;13:5885-93.

asthma represents a significant burden to both the individual patient and the wider health economy, in patients it is associated with lower mental and physical health-related quality of life and significantly impacts on presenteeism, work impairment, and activity impairment.[3,4] For the health system and wider society, uncontrolled asthma is associated with major direct and indirect costs, and when compared to well-controlled asthma, overall costs may be as much as double.[3,4]

Asthma is treated on a step-up/step-down basis to patients on the lowest effective dose of treatment.[5,6] Inhaled corticosteroid (ICS) in combination with a long-acting β2-agonist (LABA) are recommended for patients who do not achieve control with low-dose ICS alone,[5] but a significant proportion of patients (up to 60%) receiving ICS/LABA remain uncontrolled despite attempts to optimise adherence and inhaler technique.[3,4,7] Although multiple inhalers are effective, their use is associated with suboptimal adherence compared to single-inhaler therapies, therefore guidelines recommend simple regimes if possible.[8]

According to the National Institute for Health and Care Excellence (NICE) guidance, for those patients who do not achieve control with ICS/LABA, additional options include switching to a maintenance and reliever therapy (MART) regimen, increasing the dose of ICS (as part of a fixed-dose regimen), a trial of additional drug (for example, a long-acting muscarinic receptor antagonist (LAMA) or theophylline), or referral to an asthma specialist.[6] The addition of a LAMA to an ICS/LABA regime is often referred to as 'triple therapy' and is an established treatment in chronic obstructive pulmonary disease (COPD),[9] but this approach is less well established in asthma.

Asthma patients have increased bronchial smooth muscle contraction, and this is the major contributor to respiratory symptoms in asthma.[10] Bronchial smooth muscle contraction is driven by cholinergic activity, and increased cholinergic activity and smooth muscle tone may also contribute to the airway hyper-responsiveness found in asthma patients. LAMAs target the muscarinic receptors (a subtype of the cholinergic receptor) of the airways to moderate smooth muscle contraction and reduce respiratory symptoms via a different mechanism to ICS and LABAs.[10,11]

Single-inhaler medium-strength ICS/LABA/LAMA single-inhaler triple therapy (SITT) has been shown to reduce the frequency of exacerbations and improve lung function in adults with poorly controlled asthma on an ICS/LABA combination, without the potential negative impact on adherence associated with multiple inhaler devices.[8,12]

Some confusion exists regarding who should prescribe ICS/LABA/LAMA triple therapy and in which patients. This is in part due to discrepancy between guidelines, with NICE and the Global Strategy for Asthma Management and Prevention (GINA) guidelines suggesting that a trial of triple therapy is a treatment option before specialist referral but the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN, 2019) classify LAMA as a specialist therapy.[1,5,6] These differences, along with the relative nascence of triple therapy in asthma, have led to some uncertainty among primary care practitioners, and suggestions that triple therapy should be utilised much earlier in the treatment pathway than currently recommended by GINA.[13] Therefore there is a need to clarify the role of triple therapy in asthma, including how and when primary care prescribers should consider a trial, and when to refer a patient for specialist assessment.

This project aims to define the optimal prescribing of medium-strength ICS/LABA/LAMA triple therapy in adult asthma patients who are uncontrolled on ICS/LABA, to achieve improvements to asthma control and minimise NHS specialist care burden.

Methods

The Delphi technique used in this study was guided by Guidance on Conducting and REporting DElphi Studies (CREDES). Following a review of available literature conducted by an independent facilitator (Triducive Partners Limited), a steering group of UK asthma specialists from both primary and secondary care health settings convened in June 2023 to discuss aspects of asthma care and the optimal use of medium-strength triple therapy in adult asthma patients uncontrolled on ICS/LABA. The steering group was selected based on published research, and experience in the management and care of adult patients with asthma.

Using a modified Delphi methodology [Figure 1] guided by the independent facilitator, the steering group identified six main domains of focus:

A. The role of LAMA in adult asthma patients
B. Optimal role of primary care
C. Optimal role of integrated care
D. Follow-up and referral of patients
E. Benefits of triple therapy to the adult asthma pathway
F. The opportunity for future guidelines.

These domains were each discussed by the steering group and 40 statements were subsequently agreed. The steering group members reviewed the statements independently to remove, add or change any statements. Suggestions were upheld if either they provided more clarity to a statement or were agreed by a simple majority of the group. The resulting 39 statements were then used to develop the final agreed statement set for wider testing. This constituted the first round of the process.

The survey was distributed through the list of healthcare providers (HCPs) held by a third party (M3 Global Research), the identity of which was not known to the steering group and were representative of both primary and secondary care nurses, doctors and pharmacists.

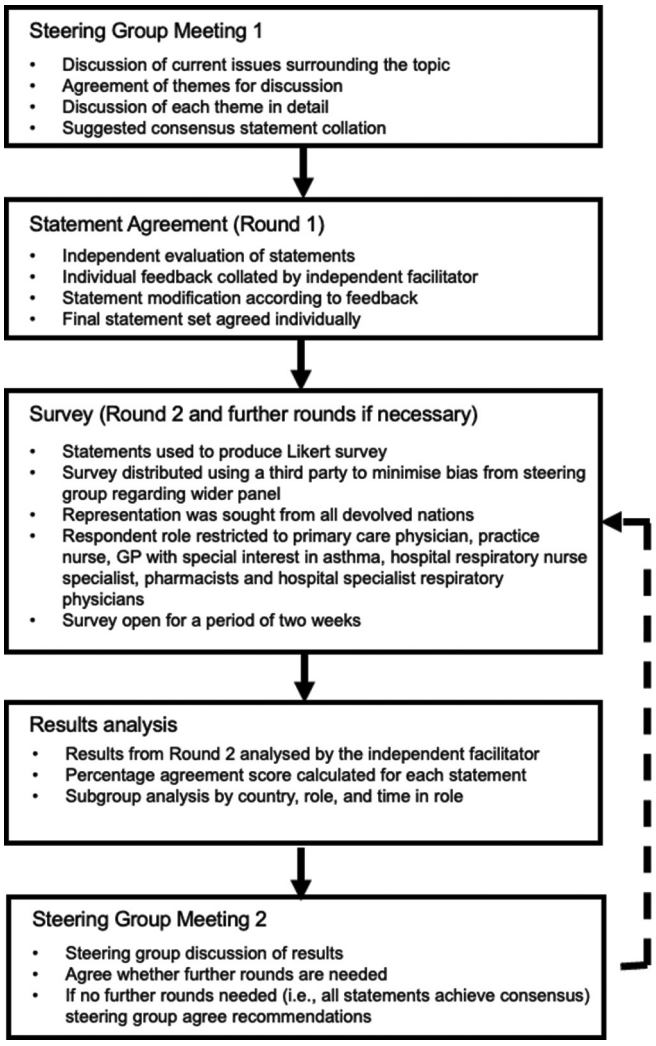

Figure 1: Modified Delphi study design. The study comprised two rounds to reach consensus on the statements included in the survey and distribute it among HCPs. The steering group convened twice to identify themes for agreement and discuss the final results

The survey presented each statement along with a 4-point *Likert* scale ('strongly disagree', 'tend to disagree', 'tend to agree', and 'strongly agree') to allow respondents to indicate their corresponding level of agreement. The survey also captured some demographic data for further analysis. Demographic data captured included respondent role, which of the devolved nations of the UK they worked in, and time in their professional role. All responses collected were included for the final analysis.

Stopping criteria were established as a two-month window to collect responses (August–October 2023), a minimum target of 300 responses within the allotted window, 90% of statements passing the threshold for consensus, and a threshold for consensus set at 75% (a widely accepted threshold[14]). Consensus was then further defined to be 'strong' at ≥ 75% and 'very strong' at ≥ 90%. These criteria were established to gain the maximum number of responses and provide stability of results while allowing in time pressures within the healthcare system.

A statement of consent was included at the start of the survey and consent was implied by completion and submission of the survey. As this study only collected the anonymous opinions of healthcare professionals and no patient-specific data was captured, ethical approval was not sought.

Completed surveys were collated and analysed by the independent facilitator to produce an arithmetic agreement score for each statement. This information was then reviewed by the members of the steering group to determine what recommendations and conclusions could be developed based on the responses received.

Results

During the first round of consensus testing with the members of the steering group, the initial set of 40 statements was critically reviewed to determine the final set of statements for wider testing. From this first round, one statement was removed, five statements were modified and agreed, no new statements were included, and 34 statements were agreed for inclusion without modification, producing a final set of 39 statements for testing with a wider panel of experts (Round 2).

The second round of testing comprised the wider body of asthma specialist HCPs within the UK. The respondent panel was selected based on a convenience sampling approach conducted utilising the list of HCP subscribers held by a third party (M3 Global Research).

Of this second round, 314 responses were collected within the survey period of which 88 were from hospital specialist doctors (specialist registrar or consultant), 75 from general practitioners, 59 from practice nurses, 47 from respiratory nurse specialists (hospital-based), 30 from pharmacists, and 15 from general practitioners with a special interest in asthma. Of these responses, 287 (91.4%) stated that they worked in England, and 251 (79.9%) stated that they had more than 5 years of experience within their role.

Results from round 2 showed very strong agreement (≥90%) in 22/39 statements, strong agreement (<90% and ≥ 75%) in 16/39 statements and failure to achieve consensus agreement threshold in 1/39 statements [Figures 2 and 3]. The finalised statements and corresponding level of agreement in round 2 are given in Table 1.

These results were shared with the steering group for analysis and discussion. As the stopping criteria were met, no further round of testing was undertaken.

Discussion

The role of LAMA in adult (≥18 years) asthma patients

There was clear agreement amongst respondents that a LAMA should be considered as an add-on therapy for those individuals

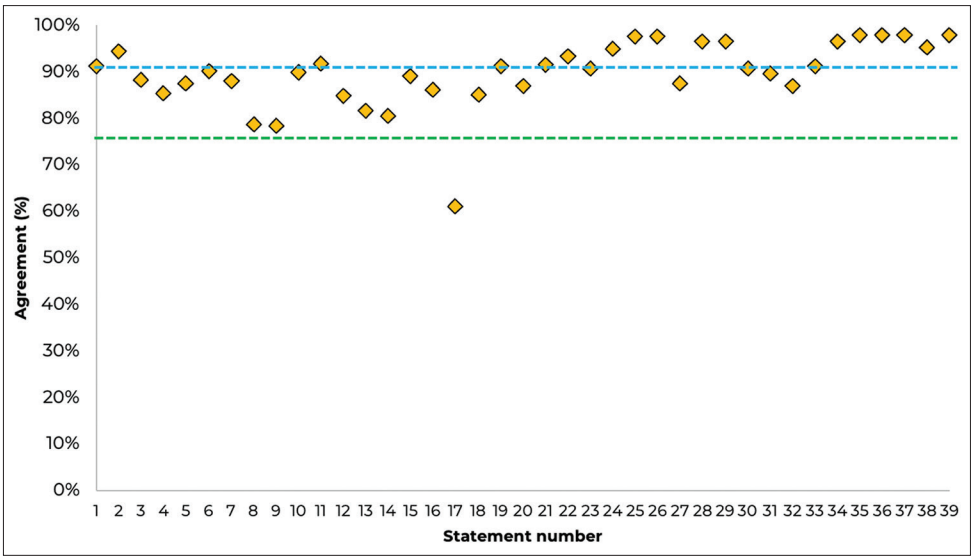

Figure 2: Combined consensus scores across 39 statements. The green line represents the threshold for consensus, and the blue line represents the threshold for very strong agreement. A very strong agreement (≥90%) was reached in 22/39 statements, while strong agreement (<90% and ≥75%) was observed in 16/39 statements. However, consensus agreement threshold was not met in 1/39 statement

who are not well-controlled on ICS/LABA (assuming adherence is acceptable and inhaler technique has been checked). All respondents roles recognised that there is a role for a LAMA in adult asthma, and that appropriate use of a LAMA can reduce exacerbations and improve lung function. This suggests that respondents are aware of the mechanism of action of LAMA treatments (possibly due to experience with use in COPD) and recognise the utility this may have inappropriate adult asthma patients. While triple therapy (ICS/LABA/LAMA) can be effective when delivered in separate inhalers, the use of multiple inhalers may contribute to suboptimal adherence.[15,16] Furthermore, SITT is associated with improved cost-effectiveness and decreased healthcare resource utilisation versus the use of multiple inhalers.[8] In patients uncontrolled on an ICS/LABA, the addition of a LAMA increased the time to the first severe exacerbation, reduced the rate of severe exacerbations and improved lung function measures.[8]

There was very strong agreement (90%) that a LAMA is appropriate for those individuals at Step 3 (BTS/SIGN, 2019: Initial add-on therapy) and strong agreement (88%) that it should be considered for use in those uncontrolled at Step 4 (BTS/SIGN, 2019: Additional controller therapies). This is in line with evidence that LABAs and LAMAs have complementary mechanisms of action to increase bronchodilation.[17]

These results suggest that there is clear support for the addition of a LAMA to ICS/LABA in patients uncontrolled at Step 3 and before referral for specialist care (Step 5 BTS/SIGN 2019),[5] but the lower agreement levels to statements regarding confidence in identification and initiation of SITT in appropriate individuals revealed a potential barrier to optimal use. When statements 8 and 9 were analysed by role, GP respondents (n = 75) had the lowest agreement rate of all roles (S8, 59%; S9, 63%). To reduce the need for referral to secondary care services and subsequent delays to treatment optimisation, GPs need to feel confident in these aspects of asthma care.

Optimal role of primary care

Statements in domain B showed good alignment that primary care practitioners are not prohibited from initiating appropriate patients on a medium-strength SITT, and that this should happen before referral to secondary care services. There is a contradiction between responses to statement 13 (82% [medium strength triple therapy should be initiated in primary care before onward referral]), and the similarly themed statement 17 (61% [patients requiring medium strength triple therapy do not need to be referred]). It could be that statement 13 is perceived as a statement of principle while statement 17 reflects practice, but the role with the lowest agreement for statement 17 was the hospital specialist doctor (n = 88, 56%). This suggests a need for more integrated care and cross-functional work to identify and mitigate some of the specific concerns that may exist around medium-strength SITT initiation by primary care services. Interestingly, the hospital specialist doctor responder group exhibited much lower levels of agreement with statement 18 (that optimal use of SITT in primary care will reduce referrals from primary care) than the other responder groups, but the reasons for this are not known.

Responders agreed that a focus on maintenance and reliever therapy (MART) in primary care may be a barrier to the optimal use of medium-strength SITT, but it should be emphasised that asthma is a heterogenous disease.[18] and there is no 'one-size-fits-all' approach to management, so prescribers should make decisions according to individual patient characteristics.

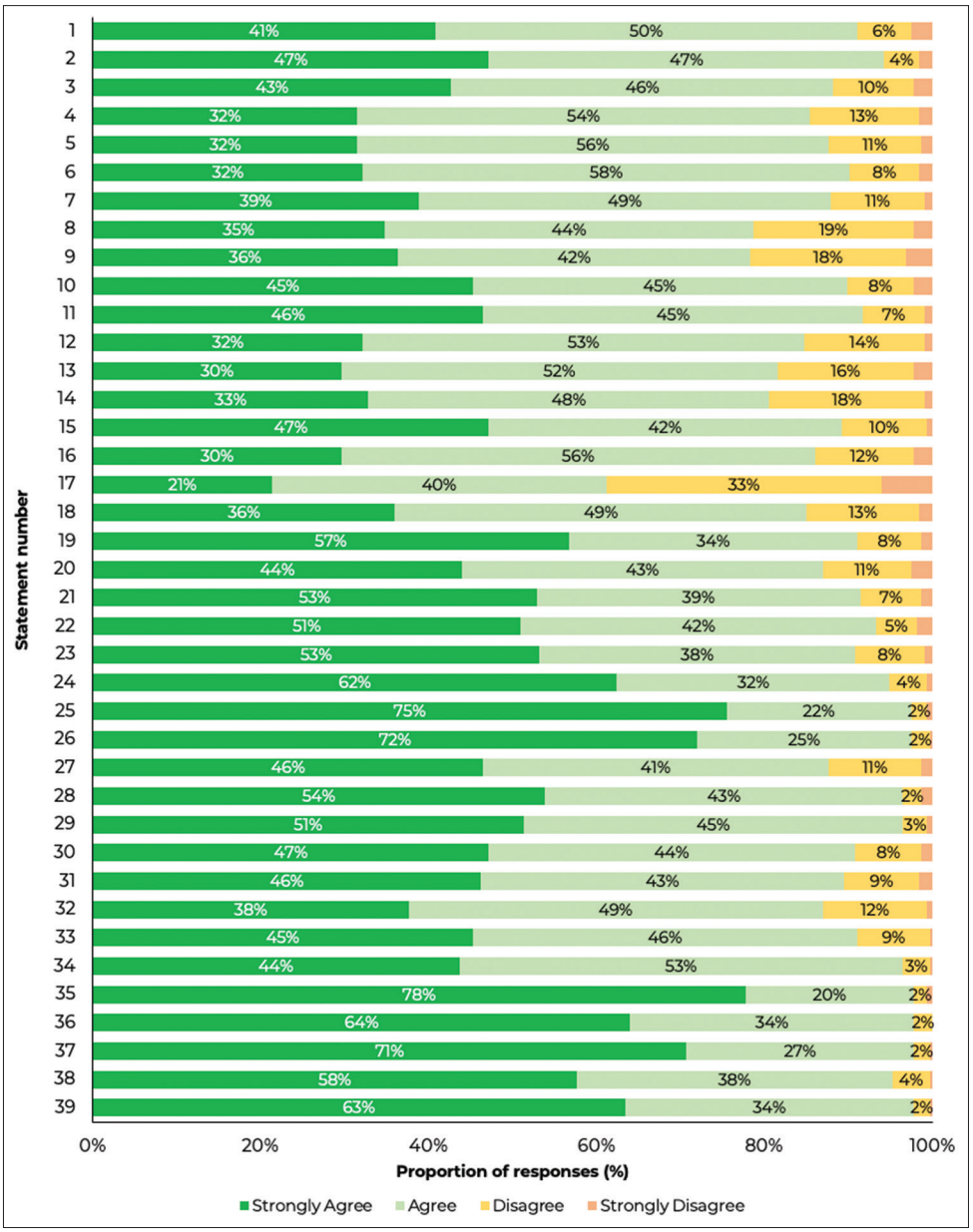

Figure 3: Consensus score distribution across the four-point *Likert* scale offered to respondents. The bar chart illustrates the percentage distribution of responses ('strongly agree', 'agree', 'disagree', 'strongly disagree') from the 314 HCPs regarding 39 statements

Optimal role of integrated care

Very strong agreement (≥90%) exists for integrated approaches to decision-making in asthma amongst all responder roles. There is a strong belief that a multidisciplinary team (MDT) approach can improve both communication between primary and secondary care clinicians and confidence in initiating medium-strength SITT (statement 22, 93%) in primary care.

Access to a respiratory specialist through a virtual MDT would be beneficial in supporting primary care in getting a patient's asthma under control before a referral to secondary or tertiary care services is needed.

Follow-up and referral of patients

Responses to statements in domain D demonstrate a clear understanding that individuals who have not gained control of their asthma despite good adherence, observed good inhaler technique and a trial of medium-strength SITT should be referred to specialist respiratory services for confirmation of diagnosis and assessment for potential severe asthma.[1,6] The key principle here is that before referral to a respiratory specialist, adherence and inhaler technique should be assessed and optimised, and appropriate add-on therapies should be trialed. As mentioned above, the 2019 BTS/SIGN guidelines categorise a LAMA as a specialist therapy (in asthma) and state that patients being considered for this 'should be referred for specialist care'.[5]

Table 1: Defined consensus statements and corresponding levels of agreement attained

Statement	Agreement
Domain A: The role of LAMA in adult asthma patients	
A LAMA should be considered for those who are on an ICS/LABA with uncontrolled adult asthma	91%
A LAMA should be considered for those who are on an ICS/LABA with uncontrolled adult asthma and persistent airflow obstruction	94%
There is a role for a single inhaler triple therapy comprising ICS/LABA/LAMA for uncontrolled adult asthma patients	88%
The LAMA component of single inhaler triple therapy (ICS/LABA/LAMA) reduces exacerbations	85%
The LAMA component of single inhaler triple therapy improves lung function	88%
Patients with uncontrolled adult asthma at Step 3 (BTS/SIGN 2019: Initial add-on therapy) should be considered for addition of a LAMA as part of medium strength single inhaler triple therapy (ICS/LABA/LAMA)	90%
Patients with uncontrolled adult asthma at Step 4 (BTS/SIGN 2019: Additional controller therapies) should be considered for addition of a LAMA as part of medium strength single inhaler triple therapy (ICS/LABA/LAMA)	88%
I am confident identifying patients who may be appropriate for a LAMA as part of single inhaler triple therapy (ICS/LABA/LAMA) in my practice	79%
I am confident initiating a LAMA as part of single inhaler triple therapy (ICS/LABA/LAMA) in my practice	78%
Addition of a LAMA as part of single inhaler triple therapy (ICS/LABA/LAMA) may provide the opportunity to optimise treatment in patients on a high-dose ICS/LABA	90%
Domain B: Optimal role of primary care	
Reducing use of high-dose inhaled corticosteroids is a goal in the management of adult asthma	92%
Primary care services are not prohibited from initiating medium strength single inhaler triple therapy (ICS/LABA/LAMA) in appropriate adult asthma patients	85%
Patients that require a LAMA as part of a medium strength single inhaler triple therapy (ICS/LABA/LAMA) should be initiated in primary care prior to any onward referral	82%
Lack of timely access to spirometry should not prevent the initiation of a LAMA	81%
Where available, within a reasonable timeframe, patients should have spirometry to confirm airway obstruction prior to initiation of a LAMA	89%
The use of MART in primary care may prevent consideration of medium strength single inhaler triple therapy (ICS/LABA/LAMA) in appropriate adult asthma patients	86%
Patients requiring a medium strength single inhaler triple therapy (ICS/LABA/LAMA) do not have to be referred to specialist respiratory services	61%
Optimal use of a LAMA as part of a single inhaler triple therapy (ICS/LABA/LAMA) in primary care will reduce the number of referrals to specialist respiratory services	85%
Primary care services should have access to spirometry (within 2 weeks)	91%
Primary care services should have access to FeNO tests (within 2 weeks)	87%
Domain C: Optimal role of integrated care	
Integrated meetings (i.e., between primary and secondary care) are an efficient way to facilitate appropriate prescribing of a single inhaler triple therapy (ICS/LABA/LAMA) in primary care	91%
The confidence of primary care initiation of a medium strength single inhaler triple therapy (ICS/LABA/LAMA) would benefit from a MDT approach which includes a respiratory specialist	93%
A virtual MDT system which includes a respiratory specialist might help to get patients' asthma under control without the need for onward referrals from primary care	91%
A virtual MDT can provide a platform for improved communication between general practitioners and specialist respiratory services	95%
Domain D: Follow up and referral of patients	
Patients who have had their medicine optimised (including the addition of a LAMA) and inhaler technique reviewed but do not have their asthma controlled should be referred to specialist respiratory care	97%
Patients at risk of a misdiagnosis should be referred to specialist respiratory care	97%
Patients with one or more co-morbidities are likely to require referral to specialist respiratory care	88%
I am confident identifying patients who should be referred to a specialist respiratory service	96%
Domain E: Benefits of triple therapy to the adult asthma pathway	
For appropriate patients, access to triple therapy in primary care will improve the patient experience	96%
For appropriate patients, access to triple therapy in primary care will reduce capacity issues in secondary care respiratory services	91%
For appropriate patients, access to triple therapy in primary care will reduce referrals to specialist respiratory care	89%
For appropriate patients, access to triple therapy in primary care will reduce the carbon footprint of asthma management	87%
Stepping up to triple therapy (by adding a LAMA) can mitigate the risk of side-effects from high-dose ICS containing medications	91%
Stepping up to triple therapy by adding a LAMA is a well-tolerated option	96%
Domain F: The opportunity for future guidelines	
Before escalating any therapy for adult asthma, triggers, adherence, and inhaler technique should be checked	98%

Contd...

Table 1: Contd...

Statement	Agreement
Domain F: The opportunity for future guidelines	
Future guidelines should be consistent in the placement of LAMA therapies and who in the NHS can prescribe them	98%
Future guidelines should provide clear patient criteria for prescribing a LAMA as part of triple therapy for adult asthma	98%
Future guidelines should advocate for competent primary care prescribing of triple therapy in appropriate adult asthma patients	95%
Future guidelines should communicate that triple therapy is licensed for use in adult asthma patients	98%

The guideline does not define what 'specialist care' means and the authors suggest that it is appropriate to consult a respiratory specialist, but this does not need to be a secondary care specialist physician. A primary care or community nurse with a special interest in respiratory medicine, a GP with a special interest in respiratory medicine, or a clinical respiratory pharmacist are examples of specialists who could support the local prescribing of LAMA/SITT therapies. This is in line with NHS England's clinically-led Speciality Outpatient Guidance, which states:

> *"Consider alternatives to acute provider by development/use of specialist-led respiratory community/integrated services"*[19]

Benefits of triple therapy to the adult asthma pathway

There was almost universal agreement that patients (96%) and the NHS (specifically secondary care respiratory services, 91%) stand to benefit from primary care prescribing of triple therapy in appropriate patients, and that triple therapy is a well-tolerated option. This suggests that most healthcare professionals working with respiratory patients are aware of the efficacy and utility of LAMAs (possibly through experience of use in COPD), and aware of the growing evidence supporting efficacy and tolerability in asthma.[12,20–22]

The authors suggest that all primary care services should consider a trial of SITT before referral to specialist respiratory services, but this should not delay the referral of patients where needed. The addition of a LAMA to ICS/LABA is associated with low-risk or tolerability concerns in individuals who have poor control of their asthma despite adherence to an ICS/LABA (with a SABA as needed). It should be stated that any change to therapy should only be carried out in patients who have had their adherence and inhaler technique reviewed, and an updated personalised asthma action plan implemented.[23]

The opportunity for future guidelines

High agreement levels for statements 36–39 demonstrate that all responder roles need clarity around the use of LAMA therapies. Any future guidelines should clearly define:

1. Where in the treatment pathway a trial of LAMA (as add-on/SITT) should be considered (i.e., before referral to secondary care specialist)
2. The patient cohort appropriate for a trial of LAMA/SITT
3. Monitoring and follow-up in primary care

Most importantly, guidelines should be consistent (BTS/SIGN, NICE, GINA) and reflect current best-practices that align with the NHS Long Term Plan to reduce reliance on secondary care services by enhancing community healthcare delivery and the use of a single inhaler (as part of SITT) in line with NHS ambitions to reduce greenhouse gas emission associated with respiratory medicine.[24]

Recommendations

Based on the results obtained during the survey phase of this study and the following discussion held by the steering group, the authors offer the following set of recommendations as to how the optimal approach for prescribing triple therapy in uncontrolled adult asthma can be achieved.

1. In adult patients with asthma that are uncontrolled on an ICS/LABA, primary care services should consider a trial of a LAMA (as part of SITT) in appropriate patients before referral to secondary/tertiary respiratory services.
2. Adults whose asthma is not controlled at Step 3 or Step 4 (BTS/SIGN 2019) should be considered for medium-strength SITT (ICS/LABA/LAMA).
3. Respiratory specialists should provide support and education to primary care prescribers to facilitate SITT use in primary care.
4. Before any change of medication or referral, patients should be fully assessed for any new symptom triggers, adherence with treatment and inhaler technique.
5. Primary care services should consider how the appropriate use of SITT can support adult patients who are uncontrolled on MART.
6. An MDT approach should be employed to support prescribing in primary care.
7. Virtual methods of communication can support the MDT in ensuring that patients get timely access to care.
8. Adult asthma patients who remain uncontrolled (despite good adherence to SITT) should be referred to a specialist respiratory service.
9. Optimal use of SITT can reduce the need for high-dose ICS inappropriate adult asthma patients.
10. The addition of a LAMA to ICS/LABA is a well-tolerated treatment option.
11. Before any referral, the patients should have their medication and adherence reviewed and optimised (including any potential new symptom triggers).
12. Future guidelines (BTS/SIGN/NICE) should clarify the use of SITT in primary care (including patient criteria).

List of abbreviations

Abbreviation	Definition
COPD	Chronic obstructive pulmonary disease
HCP	Healthcare professional
ICS	Inhaled corticosteroid
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic receptor antagonist
MART	Maintenance and reliever therapy
NICE	National Institute for Health and Care Excellence
SITT	Single-inhaler medium-strength
COPD	Chronic obstructive pulmonary disease
HCP	Healthcare professional
ICS	Inhaled corticosteroid

Acknowledgements

Name	Role
Ian Walker (Triducive Partners Ltd.)	Data analysis, manuscript writing
Tim Warren (Triducive Partners Ltd.)	Project support, meeting facilitation
Kirsten Brown (Triducive Partners Ltd.)	Project support, data collation

Ethical Policy and Institutional Review Board Statement

A statement of consent was included at the start of the survey and consent was implied by completion and submission of the survey. As this study only collected the anonymous opinions of healthcare professionals and no patient-specific data was captured, ethical approval was not sought.

Financial support and sponsorship

This study was initiated and funded by Chiesi Limited. All authors, except for Natalie Harper, received honoraria from Chiesi Limited while undertaking this study. The funder played no role in study design, data collection analysis and interpretation of data, or the writing of this manuscript. Chiesi Limited commissioned Triducive Partners Limited to facilitate the project, analyse the responses to the consensus statements in line with the Delphi methodology, and write the initial draft manuscript. Chiesi Limited reviewed the consensus statements and draft manuscript for technical accuracy only.

Conflicts of interest

Author DA-Z is involved in Treating Tobacco Dependence, Inhaler Technique, Medicines Optimisation in Respiratory Care (AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Glenmark, GSK, Johnson and Johnson, Novartis, Orion, Pfizer, Reckitt, Teva, Trudell). All other authors declare no financial competing interests.

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