BMJ Open Respiratory Research

Impact of patient support programmes among patients with severe asthma treated with biological therapies: a systematic literature review and indirect treatment comparison

Adrian P J Rabe ,[1,2] Wei J Loke ,[3] Danuta Kielar,[1] Tamsin Morris,[1] Vivian H Shih,[1] Lynda Olinger,[1,4] Mihaela G Musat,[4] Zhiyi Lan,[4] Sharada Harricharan,[4] Olivia Fulton,[5] Azeem Majeed,[2] Liam G Heaney[6]

To cite: Rabe APJ, Loke WJ, Kielar D, *et al*. Impact of patient support programmes among patients with severe asthma treated with biological therapies: a systematic literature review and indirect treatment comparison. *BMJ Open Respir Res* 2024;**11**:e001799. doi:10.1136/bmjresp-2023-001799

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjresp-2023-001799).

Received 28 April 2023
Accepted 5 April 2024

Check for updates

© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to
Dr Adrian P J Rabe; submissions@pshta.com

ABSTRACT

Introduction Effective treatment of severe asthma requires patient adherence to inhaled and biological medications. Previous work has shown that patient support programmes (PSP) can improve adherence in patients with chronic diseases, but the impact of PSPs in patients with severe asthma treated with biologics has not been thoroughly investigated.

Methods We conducted a systematic literature review to understand the impact of PSPs on treatment adherence, asthma control and health-related quality of life (HRQoL) in patients with severe asthma. Embase, MEDLINE and EconLit databases were searched for studies published from 2003 (the year of the first biological approval for severe asthma) to June 2023 that described PSP participation among patients with severe asthma on biological treatment. Direct pooling of outcomes was not possible due to the heterogeneity across studies, so an indirect treatment comparison (ITC) was performed to determine the effect of PSP participation on treatment discontinuation. The ITC used patient-level data from patients treated with benralizumab either enrolled in a PSP (VOICE study, Connect 360 PSP) or not enrolled in a PSP (Benralizumab Patient Access Programme study) in the UK.

Findings 25 records of 21 studies were selected. Six studies investigated the impact of PSPs on treatment adherence, asthma control or HRQoL. All six studies reported positive outcomes for patients enrolled in PSPs; the benefits of each PSP were closely linked to the services provided. The ITC showed that patients in the Connect 360 PSP group were less likely to discontinue treatment compared with the non-PSP group (OR 0.26, 95% CI 0.11 to 0.57, p<0.001).

Conclusions PSPs contribute to positive clinical outcomes in patients with severe asthma on biological treatment. Future analyses will benefit from thorough descriptions of PSP services, and study designs that allow direct comparisons of patient outcomes with and without a PSP.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patient support programmes (PSP) have improved treatment adherence and clinical outcomes in patients with other chronic diseases, but the impact on patients with severe asthma is unclear.

WHAT THIS STUDY ADDS

⇒ This study provides evidence of positive outcomes following PSP participation among patients with severe asthma, including higher treatment adherence or decreased discontinuation, improved asthma control and health-related quality of life, and reduced healthcare resource utilisation following PSP participation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ PSPs serve as useful tools for clinicians, offering maximised benefits when the services they provide are matched to the needs of a specific patient population. PSPs providing educational sessions are likely to improve asthma control, whereas those facilitating at-home administration of injectable biologics can reduce healthcare resource utilisation. The large-scale implementation of PSPs should be explored in research and policy to assess the benefits observed in a wider population of patients with severe asthma.

INTRODUCTION

Approximately less than 4–10% of adult and paediatric patients with asthma have severe asthma,[1–4] which requires treatment with high-dose inhaled corticosteroids, plus secondary controller medication(s) to avoid severe exacerbations.[5] In recent years, biological therapies targeting type-2 (T2)-cytokine-mediated eosinophilic airways inflammation have been approved to treat severe eosinophilic asthma, with many patients achieving positive clinical outcomes in real-world settings.[6 7]

Treatment adherence is essential in maintaining adequate, long-term control of severe

asthma. Poor adherence to asthma therapy leads to poor disease control, clinical outcomes and health-related quality of life (HRQoL); greater healthcare resource utilisation (HCRU); and increased medical costs.[8 9] Reported rates of treatment adherence among patients with asthma range from 22% to 63% for patients taking inhaled corticosteroids.[10] In a clinical trial of patients treated with inhaled corticosteroids, patients who received education on correct administration technique, the importance of adherence and disease management had higher rates of adherence at the end of the 3-month study period (mean rate of 63% vs 73%).[11]

Patient support programmes (PSP) aim to provide education, monitoring and assistance to patients with chronic diseases, with the goal of improving adherence.[12 13] PSPs are designed to support patients through several therapy-related needs: adequate medication administration, disease education support, advice on disease management and treatment reimbursement assistance.[13] PSPs can reduce HCRU and mortality in patients taking biological therapies for autoimmune disorders such as rheumatoid arthritis, Crohn's disease, psoriasis, ulcerative colitis, psoriatic arthritis, hidradenitis suppurativa, ankylosing spondylitis and uveitis.[12 14–16] However, the impact of PSPs has not been extensively investigated in patients with severe asthma.

This study aimed to identify evidence gaps regarding the impact of PSPs for patients with severe asthma via a systematic review of outcomes of PSP participation reported in patients with severe asthma following treatment with biological therapies. The secondary objective was to estimate the effect of participating in a PSP on treatment discontinuation in patients with severe asthma based on data from two UK-based studies in patients with severe eosinophilic asthma treated with benralizumab who were either enrolled in a PSP (VOICE study, Connect 360 PSP)[17] or not enrolled in a PSP (Benralizumab Patient Access Programme (BPAP)).[18]

METHODS

A systematic literature review (SLR) was conducted to identify studies reporting PSPs and other patient support activities, as well as their impact on patients with severe asthma who were treated with any of the following approved biological therapies: benralizumab, dupilumab, mepolizumab, omalizumab or reslizumab.[19] The SLR methodology followed recommendations per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[20] and by the Cochrane Collaboration, the Centre for Reviews and Dissemination and the National Institute for Health and Care Excellence (NICE).[21–23] Due to the variety in function and structure of PSPs, a working definition was developed that included PSPs from five general categories:

- Structured PSPs offering a variety of support services.
- Patient education on asthma treatment administration (inhaler and/or biological therapy) and adherence.
- A clinical multidisciplinary team approach to patient education on asthma treatment administration (inhaler and/or biological therapy) and adherence.
- At-home administration of biological therapy
- Telemedicine services.

Searches were conducted of the MEDLINE, MEDLINE In-process, Embase and EconLit databases via Ovid for studies published in English from 01 January 2003 (the first year a biological therapy was approved for asthma) to 23 June 2023. Manual searches were performed for relevant abstracts published between January 2020 and 31 July 2023 from the following conference proceedings: The Professional Society for Health Economics and Outcomes Research, American Academy of Allergy, Asthma and Immunology, American Thoracic Society, European Respiratory Society, the European Academy of Allergy and Clinical Immunology and the American College of Chest Physicians. The search strategies are provided in online supplemental table 1.

Citation tracking and snowballing techniques were used in the review process. Bibliography lists from all relevant published reviews and SLRs were cross-checked to ensure no relevant studies were missed.

Studies were screened for eligibility using the population, intervention, comparator, outcomes and study design (PICOS) criteria, which can be found in online supplemental table 2. The screening was conducted by two independent reviewers at both the title/abstract and full-text levels and a third, independent reviewer resolved any disagreements. Data were extracted into a predetermined, Microsoft Excel-based template by two independent reviewers (one of which was also involved in the screening stage) and any conflicts at this stage were resolved through consensus-based discussion or a third reviewer. Variables extracted involved study characteristics (design, country, data collection period), patient characteristics, description of patient support activities and services and measures of asthma control, HRQoL and HCRU at baseline and during the study period as well as any effect measures and observations related to the impact of PSPs on these measures. Quality assessment of studies included in the review was performed using the Newcastle-Ottawa scale for non-randomised, cohort or case–control studies[24] and its adapted version for cross-sectional studies.[25] Newcastle-Ottawa scale is a reliable tool, widely used to assess the quality of prospective or retrospective observational studies, focusing on broad areas such as study population selection and ascertainment of the outcome of interest. The adapted version of the Newcastle-Ottawa scale, previously used by Brandenberger and collaborators, provides an additional assessment of survey-specific aspects such as response rate and description of the survey tool.[25] The quality assessment for each study was performed by two independent

Table 1 Characteristics of the studies included in the indirect treatment comparison model

	Non-PSP group (BPAP study)[18]	PSP group (VOICE study)[17]
Data source	UK, retrospective cohort study based on data collected as part of routine patient care during the benralizumab patient access programme	UK, retrospective cohort study based on data collected during the Connect 360 PSP
Study period	April 2018 to July 2019	October 2019 to September 2021
Population	Patients with severe eosinophilic asthma treated with benralizumab	Patients with severe eosinophilic asthma treated with benralizumab
Definition of discontinuation	Discontinuation documented by the treating physician in the medical chart	Defined as a gap of >9/>12 weeks since the last delivery date, with the date of benralizumab discontinuation defined as the last delivery date +9/+12 weeks and 1 day
Index date	First administration of benralizumab	PSP enrolment date
Timepoint of assessment of discontinuation	48 weeks since index date	48 weeks since index date

BPAP, Benralizumab Patient Access Programme; ITC, indirect treatment comparison; PSP, patient support programme; UK, United Kingdom.

reviewers, with conflicts resolved through discussions until a consensus was reached.

Indirect treatment comparison to estimate the effect of PSP participation on treatment discontinuation

A meta-analysis of the studies describing PSP impacts was not feasible due to differences in PSP and study designs, and participants. Instead, an indirect treatment comparison (ITC) was performed to determine the effect of PSP participation on biological treatment discontinuation using patient-level data from two UK-based studies: the VOICE study, in which patients were enrolled in the Connect 360 PSP,[17] and the BPAP study, which did not include a PSP. The characteristics of the studies used in the ITC are shown in table 1. In the UK, benralizumab is indicated as an add-on maintenance treatment for adults with severe eosinophilic asthma inadequately controlled with high-dose inhaled corticosteroids plus long-acting β-agonists.[26] Benralizumab is given as an injection every 4 weeks for the first three doses, and every 8 weeks thereafter.[27]

Following the market authorisation of benralizumab, patients who were identified by their treating respiratory clinicians as requiring access to benralizumab due to clinical need were provided with benralizumab at no cost to the National Health Service (NHS) based on the license criteria, until national reimbursement was available through NICE.[18] Patients enrolled in BPAP from April 2018 to June 2019 received benralizumab administration under routine clinical practice methods without a PSP.[18 28]

The VOICE study included only patients enrolled in the Connect 360 PSP between October 2019 and September 2021.[17] Connect 360 PSP was designed to support patients with severe asthma in the at-home administration of benralizumab and to equip patients with the skills and confidence to self-inject.[17] Additionally, the programme aims to support patient adherence, improve patient HRQoL and asthma control, reduce the HCRU burden and expand capacity in severe asthma centres.[17] Connect 360 provides reimbursement services, injection services and clinical support.[17] Patient demand for the services provided through Connect 360 was supported by the publication of the NICE guideline calling for at-home treatment for severe asthma during the coronavirus disease 2019 (COVID)-19 pandemic.[29 30]

To estimate the effect of PSP participation on treatment discontinuation, logistic regression with inverse probability of treatment weighting (IPTW) was used, with propensity scores representing the probability of treatment (enrolment in PSP) given measured baseline characteristics (age and previous biological exposure). The non-PSP group comprised patients enrolled in BPAP and the PSP group was composed of patients enrolled in VOICE Connect 360. The data collection protocols of each study are shown in online supplemental figure 1. Patients in the VOICE study who received their first benralizumab injection prior to 1 July 2019 could have participated in the BPAP study, and thus were excluded from the Connect 360 PSP group in the analysis to avoid overlap in PSP and non-PSP participants. The analysis included patients with at least 48 weeks of possible follow-up time from the respective study index dates (the date of enrolment in Connect 360 for VOICE and the date of first benralizumab injection for BPAP). The statistical approach adjusted for age and prior exposure to biologics (table 1) with discontinuation of benralizumab as the dependent variable. In the BPAP study, treatment discontinuation was recorded at the discretion of the treating physician, whereas the VOICE study defined treatment discontinuation as a 9-week gap in benralizumab administration.

To better explore the influence of sex, treatment discontinuation definition and prior biological exposure, sensitivity analyses were conducted under three scenarios:

1. Sex was included with age and prior biological treatment experience in the IPTW model.

2. In the Connect 360 PSP group, discontinuation was defined as a 12-week gap in benralizumab administration, instead of a 9-week gap.
3. Only patients with prior exposure to biologics were included in the analysis.

The results of the ITC were generated as ORs with 95% CIs. All analyses were done in R V.4.2.0.

Changes from the registered protocol

The study protocol was registered to PROSPERO (ID CRD42022316289). The original searches were conducted on 16 September 2021 and were updated, most recently, on 23 June 2023. After the review of the full text of all citations selected at title/abstract screening, an additional exclusion criterion was applied to remove all studies that enrolled fewer than 10 patients. The original scope of the SLR also included the identification of studies not involving PSPs that could be considered relevant comparators in the ITC versus the VOICE study. However, the ITC technique deemed suitable for this analysis required patient-level data from the studies being compared. For this reason, the ITC was performed on the VOICE and BPAP studies; both enrolled patients with severe asthma who were treated with benralizumab, were conducted in a similar healthcare setting, and used patient-level data to which the authors had access.

Patient and public involvement

Although patients and the public were not involved in the design and execution of this study, the perspective of a patient with severe asthma was included in this article as a coauthor (box 1). We expect our findings will be disseminated through patient engagement and advocacy for PSPs, which carry the intent for patient-centric care in their design.

Box 1 Patient perspective on the relevance and utility of patient support programmes (PSPs) in severe asthma treated with biological therapies, by patient author Olivia Fulton.

As a patient with severe asthma who is enrolled in a biological programme under the care of specialists in Scotland, I have first-hand experience with biological treatment and support programmes. The primary service offered by my PSP is the ability to contact knowledgeable severe asthma nurses by phone to ask questions about biologics and self-administration. Non-urgent questions are welcome, as are questions regarding the logistics of storing and using biologics. I have called to inquire about treatment side effects and other clinical concerns. Patients may get anxious about self-administration or fear they are doing it incorrectly, and question what would happen. Having a person to reassure you is very important. Because biologics are expensive therapies with narrow criteria for prescription, patients may feel guilty about mistakes made during self-administration and worry that they may be moved off treatment if anything goes wrong. The cost of providing PSPs should be considered in the context of patient need, which drops dramatically following the initial transition to home administration. Patients who have been on therapy for a while probably will not need support unless something new comes up. Additionally, behavioural interventions that offer support for environmental and lifestyle changes could improve quality of life and promote optimal clinical outcomes with pharmacological treatments. One potential improvement for PSPs could include giving patients the option to meet each other virtually or in person. The experience of self-administering biologics can be isolating, and peer support provides an opportunity to share the experience and to ask questions—particularly those that are minor, more personal or otherwise unlikely to be brought to a clinician. As patients become more experienced with self-administration, they may rely on peer support more than other PSP services. For patients with severe asthma, PSPs can reduce treatment anxiety and ease the transition to at-home administration. Incorporating patient feedback into PSP development and implementation may result in more useful and effective programmes.

Results

The SLR identified 25 records from 21 unique studies that were eligible for inclusion in the study. The flow of literature is presented as a PRISMA diagram in figure 1.

The studies were from 14 countries across six PSP categories (online supplemental figure 2). All the approved biologics included in the search strategy were represented in the study findings. Sample sizes ranged from 23[31] to 746,[17] and included both paediatric[31] and adult[17 32–37] patients. Characteristics of the included studies are summarised in table 2. Most of the studies published as full-text journal articles demonstrated moderate quality of reporting according to Newcastle-Ottawa Scale and its adapted version for cross-sectional studies (online supplemental table 3), fulfilling between 4 and 5 quality criteria out of the 7 applicable. The study populations included were often found to be somewhat representative of the average patients with severe asthma in the community, with one exception which included a specific group of patients with chronic rhinosinusitis.[38]

However, a few studies, including the ones published as conference abstracts, reported a short follow-up (less than 6 months),[31 37–41] or did not provide information about the patients lost to follow-up.[31 33–36 40–43] Among the cross-sectional studies, only, a study by Reed *et al*, published as a conference abstract, provided insufficient methodological details.[44]

Only six studies investigated the impact of PSPs on patient adherence, HRQoL, asthma symptom control or HCRU.[17 31–37 45] The study characteristics, outcomes assessed, results and limitations of each of the six studies are presented in table 3. The six studies could not be evaluated using meta-analysis due to differences in study design, patient population, type of PSP and interventional medications. The characteristics and findings of the six studies that provided findings on the impact of PSPs are presented below.

Characteristics of PSPs

All six studies included an educational component for patients in PSPs. Five provided instructions on proper

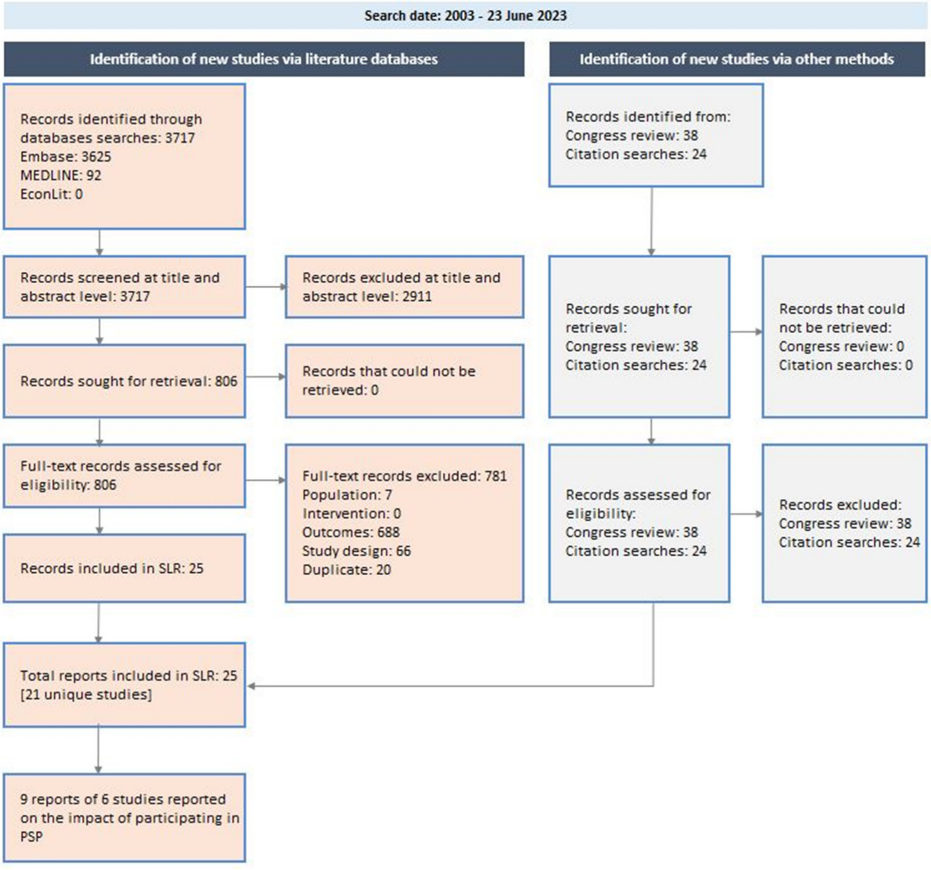


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram. PSP, patient support programmes; SLR, systematic literature review.

medication administration,[17 31 33–37 45] and four included messages on the importance of adherence.[17 32–37] In one study, the PSP provided educational sessions to children with severe asthma and their caregivers to help them transition from in-hospital to at-home administration of biologics (omalizumab/mepolizumab).[31] This was paired with virtual supervision of at-home injections and spirometry by clinical nurse specialists.[31] Patients were provided with electronic monitoring equipment when there were concerns about non-adherence to oral corticosteroids.[31]

In another study, patients with severe asthma and comorbidities were provided with refined treatment action plans as part of the PSP and had access to a multidisciplinary team of clinicians, including a dietitian, psychologist, nicotine addiction specialist and a social worker.[45]

Outcomes assessed in relation to PSP participation

Clinical measures including forced expiratory volume in one second (FEV_1), fractional inhaled nitric oxide and/or peak flow were reported by four studies.[17 31 32 45] All reported either the number of emergency room (ER) visits, hospitalisations, scheduled or unscheduled healthcare visits or a combination of these; these studies also measured asthma control using the Asthma Control Test (ACT).[17 31 33–36 45] Additional questionnaires used were the Asthma Control Questionnaire (ACQ),[17 32 37] WHO Quality of Life Assessment short version (WHOQOL-BREF),[33] Asthma Quality of Life Questionnaire for QoL (AQLQ),[37] Paediatric Asthma Quality of Life Questionnaire for QoL (PAQLQ)[31] and Treatment Satisfaction Questionnaire for Medication-9 item (TSQM-9).[17]

Two studies reported measures related to oral corticosteroid use.[17 45] Two studies reported treatment adherence, one of which defined it as the proportion of enrolled patients who filled 80% or more of their prescriptions[32]; the second study did not define treatment adherence.[33–36] Only one study measured treatment discontinuation.[17]

Adherence and treatment discontinuation outcomes

Three studies reported on oral corticosteroid use. In a study that evaluated patients on step 5 asthma therapy (as defined by the Global Initiative for Asthma [GINA]) oral corticosteroid use was significantly reduced following PSP participation.[45] In another study, there was a numerically smaller percentage of patients using maintenance oral corticosteroids at week 48 of PSP participation compared with baseline (34.8% at week 48, n=302 vs 48.4% at baseline, n=186).[17] No change in oral corticosteroid use over the study period was observed in the third study.[31]

High adherence (85%) was observed in a study that evaluated patients who received treatment with omalizumab

Table 2 Overview of included studies

Study type (size)	Country	Intervention	Population	Description of patient support services
Retrospective (N=746)[17]	UK	Benralizumab	SEA, adults, mean age 54 years	- The Connect 360 programme provided patients with education on self-administration, support for at-home administration and adherence support from trained nurses.
Prospective observational (N=104)[39]	USA	Dupilumab	SA, age ≥12 years, mean age 51 years	- Patients completed surveys for clinical and HRQoL outcomes at baseline and at regular intervals after treatment initiation; PSP description is not provided.
Retrospective (N=50)[37]	Italy	Omalizumab, mepolizumab, benralizumab, dupilumab	SA, adults, mean age 52 years	- Training for at-home administration, telephone support and remote monitoring were provided and medication was delivered at home. - Emotional and psychological support to help reduce fear and anxiety. - Patients treated with benralizumab participated in Connect 360 PSP. - Majority of patients treated with mepolizumab participated in 'Aria di Casa' PSP. For patients unable to self-inject at home, a nurse was appointed to assist with at-home medication delivery and administration.
Prospective observational (N=17)[52 53]	Argentina	Omalizumab	SA, paediatric patients, age ≥6 years, mean age 12 years	- Special healthcare modality providing frequent visits, provision of medications at no charge, the development of educational activities. - Education on environmental control (eg, tobacco use at home and household environmental contaminants), administration techniques and treatment adherence. - Psychologist-coordinated and physical therapist-coordinated sessions for exercise, physical therapy and relaxation techniques.
Retrospective (N=119)[45]	France	Omalizumab, other therapies (no other biologics)	SA, mean age 51 years	- Nurses instructed each patient on proper inhaler administration technique and provided a written action plan. - Access to a dietitian, a psychologist, a nicotine addiction specialist or a social worker. - Comorbidity interventions: pulmonary rehabilitation, nocturnal ventilation for obstructive sleeping apnoea, smoking cessation, psychiatric care, nutritional follow-up by a dietitian, sleeve gastrectomy, hyperventilation treatment.
Prospective observational (N=237)[33–36]	Colombia	Omalizumab	SA, mean age 36 years	- Educational courses provided monthly by a pharmacist, focusing on proper medication usage and the importance of adherence.
Prospective observational (N=50)[32]	UK	Mepolizumab	SA, mean age NR	- Educational sessions provided by a pharmacist focusing on the importance of adherence for patients starting biological therapy. - Nurses reiterated adherence messages during each visit.
Survey (N=54)[54]	Saudi Arabia	Omalizumab, Mepolizumab, Dupilumab	SA, mean age 47 years	- Patients responded to a cross-sectional survey that inquired about their experiences with telemedicine during the COVID-19 pandemic.
Registry (N=NR)[55]	Denmark	NR	SA, mean age NR	- An application allowing remote collection and monitoring of PROs. An upcoming expansion of the smartphone application will monitor the at-home administration (reminders for patients, administration records, side effects and an action plan for exacerbations).
Prospective observational (N=19)[43]	Russia	Omalizumab	Asthma, paediatric, mean age 14 years	- A patient-to-doctor interface was developed allowing remote telecommunication. - Patients can ask questions, enter peak flow levels, symptoms, basic therapy and rescue medication, and symptoms. - Specialists can access data on patient condition, adherence and asthma control.
Survey (N=167)[56]	Italy	Mepolizumab, omalizumab, benralizumab, dupilumab	SA, adults, treated with biologics, mean age 55 years	- Telemedicine programme including quarterly virtual visits, providing patients with spirometer and oxyhaemoglobin saturation metre for at-home measurements. - Patients will be trained on self-administration and performing measurements at home.

Continued

Table 2 Continued

Study type (size)	Country	Intervention	Population	Description of patient support services
Survey (N=120 physicians, 432 patients)[57]	Germany	Omalizumab	SA, mainly adults, mean age NR	- Multiple-choice survey aimed at understanding how patients regarded the potential at-home administration of biologics, including the level of support they would require to participate in at-home administration.
Prospective, observational (N=25)[42]	USA	Omalizumab	SEA, adults, mean age NR	- Education on self-administration.
Survey (N=26)[44]	Australia	Mepolizumab	SEA, mean age NR	- Education and training for transitioning to at-home administration.
Qualitative interviews (N=75)[58]	Netherlands, USA, Australia, Northern Ireland	Benralizumab, dupilumab, mepolizumab, omalizumab, reslizumab	SA, adults, mean age 50 years	- The interviews provided insight into the perceptions and experiences of patients and their healthcare providers on at-home administration of biologics for severe asthma. All patients received information and training before transitioning to at-home administration.
Prospective observational (N=10)[38]	Italy	Mepolizumab, dupilumab, omalizumab, benralizumab	SA and chronic rhinosinusitis with nasal polyps, adults, mean age NR	- Patients received training for self-administration and they could communicate to a dedicated nurse in case of questions, concerns or for reporting adverse events.
Prospective observational (N=33)[59]	Portugal	Omalizumab, mepolizumab, benralizumab, dupilumab	SA, adults, mean age 44 years	- Patients were given a questionnaire to assess their acceptance of the at-home administration, perceptions and concerns. - Patients were trained at the hospital to self-administer the biologic. - Patients were provided with information support (video or written).
Prospective observational (N=24)[60]	Netherlands	Reslizumab	SEA, adults, mean age 55 years	- Respiratory nurses administered at-home treatment and planned upcoming visits. - Patients had access to appointment schedules through a patient portal. - Patients could record symptoms using ACQ via a portal or personal email.
Prospective observational (N=23)[31]	UK	Omalizumab/ mepolizumab	SA, paediatric patients, median age 14 years	- Paediatric patients and caregivers were educated and supported on the at-home administration and at-home FEV_1 and FVC monitoring. - Subsequent injections, asthma control and HRQoL were virtually supervised by a clinical nurse specialist; quarterly appointments with consultants occurred virtually.
Prospective observational (N=246)[40]	UK	Benralizumab	SEA, mean age NR	- Patients were surveyed for ACQ-6 responses via telephone, following the transition to homecare.
Prospective observational (N=87)[41]	UK	Mepolizumab	SEA, mean age NR	- ACQ-6 was measured in the clinic, and then later by telephone following the transition to homecare.

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HRQoL, health-related quality of life; IgE, immunoglobulin E; NR, not reported; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; PROs, patient-reported outcomes; PSP, patient support programme; SA, severe asthma; SEA, severe eosinophilic asthma; SLR, systematic literature review.

following PSP participation, and most people used their medication correctly (90%).[33–36] Another study measured patient adherence for 12 months of PSP participation; 90% of patients with severe asthma were considered adherent, having collected more than 80% of their preventer inhaler prescriptions.[32] This proportion was notably higher than the proportion of adherent patients with severe asthma treated with omalizumab at the same hospital before implementation of the PSP (50.6%).[32 46]

Discontinuation rates of benralizumab were low following Connect 360 programme participation,[17] with 3.0% and 5.8% discontinuing treatment at 24 and 48 weeks, respectively.[17]

Disease control, HRQoL and clinical outcomes

One study reported that following PSP participation, a significantly higher proportion of patients achieved an ACT score of ≥20, indicating well-controlled asthma.[45] This result was seen in patients with asthma-related comorbidities, patients who underwent step-up asthma treatment to step 5 therapy (as defined by GINA), and patients with severe asthma with neither comorbidities nor step 5 interventions.[45] Three additional studies reported improvements in asthma control as measured by the ACQ or ACT.[17 31 35] Two studies noted a significant reduction in the number of hospitalisations following PSP participation,[34 45] one of which also reported fewer ER visits.[36] Significant improvements in patient HRQoL were found in paediatric patients using the PAQLQ[31] and adults using the WHOQOL-BREF.[33]

Table 3 Characteristics of PSPs described in studies of their impact

Reference	Population (N)	Intervention	Results	Limitations
Bègne *et al*[45]	Severe asthma (119)	Group 1: ▶ Omalizumab (N=25). ▶ Azithromycine (N=8). ▶ Bronchial thermoplasty (N=10). ▶ Oral corticosteroids (N=4). ▶ Azathioprine (N=2). Group 2: ▶ Pulmonary rehabilitation (N=3). ▶ Nocturnal ventilation for obstructive sleeping apnoea (N=4). ▶ Smoking cessation (N=1). ▶ Psychiatric care (N=1). ▶ Nutritional follow-up (N=1). ▶ Sleeve gastrectomy (N=1). ▶ Hyperventilation treatment (N=7). Group 3: ▶ No step 5 treatments ▶ No comorbidity treatments	▶ All three groups had increases in the proportion of patients to achieve an ACT score of 20 or more, indicating asthma control. In Group 1, 8.1% of patients had scores of ≥20 at baseline, compared with 19% at 6 months and 22.4 at 12 months. The same values were 0 at baseline, 6.2% at 6 months, 12.5% at 12 months for Group 2, and 11.1% at baseline, 20% at 6 months, and 29.6% at 12 months for Group 3. ▶ Three patients in Group 3 did not receive any add-on therapies but still improved asthma control, indicating that patient education alone can result in positive outcomes. ▶ There was a significant reduction in the number of patients with hospitalisations for all three groups combined (25.2% at baseline compared with 8.4% at 12 months, p<0.001). ▶ There were no significant changes in FEV1. Oral corticosteroid use significantly decreased overall and in Group 1, but there was no change in the proportion of patients receiving maintenance oral corticosteroids.	Groups 1 and 2 were heterogenous, complicating the interpretation of study results.
Estrada *et al*[33–36]	Persistent severe asthma (237)	Omalizumab	▶ ACT scores improved from a mean of 17.5 at baseline to 22.1 after 1 year (p<0.0001). ▶ HRQoL (as measured with the WHOQOL-BREF) improved in 69% of cases (from mean 67 at baseline to 77 after 1 year, p=0.028), especially in the social-environmental dimension. ▶ The proportion of patients who had at least one emergency (defined as a use of emergency services due to asthma exacerbation) decreased from 21% before the educational programme to 14% after (p=0.045). The number of emergencies per 100 patients was 40 before and 24 after programme implementation (p=0.04). ▶ The proportion of patients with hospitalisations decreased from 14.8% in the year preceding the study to 8% in the year following the study. ▶ Of the patients who were categorised as having uncontrolled asthma at baseline, 57% had well-controlled asthma and 21% had fully-controlled asthma at the end of the study period (p<0.000). ▶ The perception of healthcare improved in 70% of patients.	The role of the PSP in achieving positive patient outcomes is unclear.
Elsey *et al*[32]	Severe asthma[56]	Prevention inhaler to accompany mepolizumab	▶ After 12 months, 10% of patients were non-adherent (collected less than 80% of their inhaler prescriptions). The non-adherent patient group had a higher ACQ-7 score at 12 months, indicating less asthma control.	The impact of the PSP on patient adherence is unclear and is discussed only in the conclusions.
Makhecha *et al*[31]	Severe asthma, paediatric[23]	Mepolizumab Omalizumab	▶ FEV1, oral corticosteroid use, and the number of unscheduled healthcare visits were maintained after 3 months of participation. ACT scores improved from a median of 18 (IQR 13–22) to 23 (IQR 19–24), p=0.00005. PAQLQ scores improved from a median of 6.5 (range 4.6–6.8) to 6.6 (range 6.3–6.8), p=0.003. Patient and caregiver responses were quite positive.	The short duration of the study and the small sample size resulted in an inability to statistically compare some variables (oral corticosteroid use, the number of hospital visits, and outpatient visits).

Continued

Table 3 Continued

Reference	Population (N)	Intervention	Results	Limitations
Morris *et al*[17]	Severe eosinophilic asthma, adults, (746)	Benralizumab	▲ Mean ACQ-6 score improved from a baseline of mean 2.7 (SD 1.5, n=186) to 1.6 (SD 1.3, n=302) after 48 weeks. ▲ The proportion of patients using oral corticosteroids was reduced, from 48.4% at baseline (n=186) to 34.8 (n=306). ▲ Treatment discontinuation rates were low: 3.0% and 5.8% of evaluable patients discontinued benralizumab at 24 and 48 weeks, respectively.	Some discontinuations occurred before the study index date. There were low data capture rates for some baseline variables (oral corticosteroid use, ACQ-6 scores).
Benfante *et al*[37]	Adults with severe asthma treated with biological agents[56]	Omalizumab (14%), mepolizumab (22%), benralizumab (60%), dupilumab (4%)	▲ Transition to self-administration and home monitoring with support from PSPs did not impact patient's outcomes and enabled efficient and continued care for patients with severe asthma during COVID-19 pandemic. ▲ Mean ACT score before and after introduction of at-home administration and PSPs were 17.8 and 18.4, respectively. ▲ Mean ACQ score before and after introduction of at-home administration and PSPs were 1.58 and 1.48, respectively. ▲ Mean AQLQ score before and after introduction of at-home administration and PSPs were 4.57 and 4.59, respectively.	No formal statistical methods were applied to compare the outcomes before and after at-home administration. The effect of participating in the PSPs is unclear as it can be confounded by other factors.

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; FEV_1, forced expiratory volume in one second; GINA, Global Initiative for Asthma; HRQoL, health-related quality of life; IgE, immunoglobulin E; N, number; NR, not reported; PAQLQ, Paediatric Asthma Quality of Life Questionnaire; PRO, patient-reported outcome; PSP, patient support programme; WHOQOL-BREF, WHO Quality of Life assessment short version.

Two studies reported no changes in FEV_1 over the study period.[31 45] In a third study, asthma control was maintained during the transition to home monitoring and PSP participation.[37] Additional clinical findings are presented in table 2.

Effect of PSP participation on treatment discontinuation: BPAP vs VOICE ITC

The ITC using IPTW compared the rates of treatment discontinuation in the PSP group (n=253, mean age 53.7) and non-PSP group (n=206, mean age 50.6 years). Before initiating benralizumab, 1.2% of patients in the PSP group and 56.8% in the non-PSP group had not been exposed to any other biological treatment for asthma (table 4). The odds of discontinuing benralizumab were 74% lower in the PSP group compared with the non-PSP group (OR 0.26, 95% CI 0.11 to 0.57, p<0.001, table 4). The discontinuation rates at 48 weeks were 5.9% (15/253) in the VOICE Connect 360 PSP group and 16.0% (33/206) in the BPAP non-PSP group.

Sensitivity analyses were conducted for three scenarios: (1) adjusted for sex in addition to age and previous biological exposure; (2) a 12-week discontinuation period instead of a 9-week period; and (3) only patients with prior exposure to biologics, adjusted for age. All three scenarios demonstrated the same statistically significant trend of lower discontinuation rates in the PSP group compared with the non-PSP group (table 4).

DISCUSSION

This study is the first to provide insight into the impact of participating in a PSP for patients with severe asthma treated with biological therapies. Previous research has shown the advantages of PSP participation for patients with other chronic diseases, such as various autoimmune chronic conditions including improved adherence to treatment, improved clinical outcomes and reduced HCRU.[12 14–16]

The six studies that reported the impacts of PSP participation generally noted improvements in treatment adherence, clinical outcomes and HRQoL. The ITC estimated that participation in a PSP was associated with a reduced treatment discontinuation of 74% in a population with severe eosinophilic asthma treated with benralizumab. These findings indicate that PSPs can improve patient adherence and persistence to treatment, thereby improving asthma control and other clinical outcomes.

The benefits of PSP participation varied across the six studies that described their impact and were closely associated with the type of services provided by each PSP. Severe asthma has a complex pathology, often requiring an equally complex management plan to target primary disease as well as associated comorbidities. The multidisciplinary approach of the PSP described by one study is an example of how to support patients with comorbid conditions.[45] Educational courses, sessions and interviews were effective in eliciting better asthma control.

Table 4 Results of the ITC of discontinuation rates between the PSP group (VOICE study) and the non-PSP group (BPAP study)

	Non-PSP group (BPAP study)[18]	PSP group (VOICE study)[17]
Primary analysis		
Number of patients	206	253
Variables included in IPTW		
Age at index, mean (SD)	50.6 (14.4)	53.7 (14.3)
Age at index, median (IQR)	51.9 (41.4–60.0)	55.8 (43.7–62.8)
Bio-naïve status, naïve, n/N (%)	117/206 (56.8)	3/253 (1.2)
Outcome measure		
Discontinuation at 48 weeks*, n/N (%)	33/206 (16.0)	15/253 (5.9)
Effect of PSP (logistic regression with IPTW as weight) OR (CI)	Ref	0.26 (0.11 to 0.57)
P value	Ref	<0.001
Scenario: Include gender along with age and prior biological exposure status		
Number of patients	206	103
Variables included in IPTW		
Age at index, mean (SD)	50.6 (14.4)	53.6 (14.2)
Age at index, median (IQR)	51.9 (41.4–60.0)	55.8 (44.9–62.8)
Female n/N (%)	131/206 (63.6)	64/103 (62.1)
Bio-naïve status, naïve, n/N (%)	117/206 (56.8)	3/103 (2.9)
Outcome measure		
Discontinuation at 48 weeks*, n/N (%)	33/206 (16.0)	7/103 (6.8)
Effect of PSP (logistic regression with IPTW as weight), OR (CI)	Ref	0.25 (0.08 to 0.73)
P value	Ref	0.011
Scenario: Use a 12-week discontinuation rule instead of the 9-week rule for the PSP group		
Number of patients	206	253
Variables included in IPTW		
Age at index, mean (SD)	50.6 (14.4)	53.7 (14.3)
Age at index, median (IQR)	51.9 (41.4–60.0)	55.8 (43.7–62.8)
Bio-naïve status, naïve, n/N (%)	117/206 (56.8)	3/253 (1.2)
Outcome measure		
Discontinuation at 48 weeks*, n/N (%)	33/206 (16.0)	12/253 (4.7)
Effect of PSP (logistic regression with IPTW as weight), OR (CI)	Ref	0.20 (0.09 to 0.46)
P value	Ref	<0.001
Scenario: Only include patients with prior exposure to biological therapies		
Number of patients	89	250
Variables included in IPTW		
Age at index, mean (SD)	49.5 (14.1)	53.8 (14.1)
Age at index, median (IQR)	52.3 (38.6–59.9)	55.8 (44.7–62.8)
Outcome measure		
Discontinuation at 48 weeks*, n/N (%)	14/89 (15.7)	15/250 (6.0)
Effect of PSP (logistic regression with IPTW as weight), OR (CI)	Ref	0.40 (0.18 to 0.88)
P value	Ref	0.022

BPAP, Benralizumab Patient Access Programme; IPTW, inverse probability of treatment weighting; ITC, indirect treatment comparison; n/N, number; PSP, patient support programme.

The patients who received educational services only[33–36 45] observed improvements in asthma control as measured by the ACT. There were also reductions in hospitalisations and ER visits, another indicator of improved asthma control.[33–36 45] Patients who received assistance, training and/or supervision for the at-home administration of biologics[17 31–36] generally had higher adherence to treatment. These findings also demonstrated that a PSP can facilitate the transition from in-hospital injections of biologics to at-home administration.[17 31]

This research highlights the plethora of services PSPs can offer to address patient adherence. More thorough descriptions of PSPs in future studies would be beneficial for making comparisons and tailoring new PSPs to patient needs. Additional considerations, such as culturally informed educational components for patient subpopulations, may improve the outcomes observed following PSP participation.[47] Unintentional non-adherence to treatment is common in patients with asthma but can be improved through participation in PSPs that feature educational programmes and clinician support.[48 49] Smartphone-based applications, medical devices and teleconsultations are increasingly used to improve patient adherence and reduce HCRU, particularly as healthcare systems incorporate new patient support paradigms brought about by the COVID-19 pandemic.[50 51] PSPs that include access to these tools are well situated to facilitate the at-home administration of treatments and to reduce in-person HCRU.

Strengths and limitations

Our analysis provides a comprehensive overview of the outcomes of patients with severe asthma treated with biological therapies who participate in a variety of PSPs.

Although the SLR was conducted using rigorous methodology, the amount of relevant data were sparse and many publications only published findings in conference abstracts, which provide only limited methodology and results description. Full-text journal publications showed moderate reporting quality with occasional issues related to population representativeness or adequacy of follow-up. Most of the studies were not designed to analyse the impact of participating in a PSP. For example, patients were followed only after enrolment in the programme, which prevented the calculation of the effect of PSPs on clinical outcomes in combination with other study limitations. The identified studies did not report the costs of PSPs and did not provide information on the usefulness of PSPs within a cost-effectiveness framework. Given the evolution of patient support, including technology, there is a need to evaluate the financial, human resource, and opportunity costs of PSPs.

Given the lack of comparative studies investigating the impact of PSPs in this population, our ITC analysis provides unique insights into the potential effects of participating in a PSP on the rate of treatment discontinuation. The main advantage of the chosen approach was the use of patient-level data which allowed for the balancing of key characteristics, including age, sex and prior use of biologics between the PSP and non-PSP groups through IPTW, in an effort to minimise bias. The patient populations in the BPAP non-PSP group and VOICE Connect 360 PSP group were both treated with benralizumab in the UK healthcare setting and were similar in baseline characteristics (eg, age, sex). However, the populations differed in previous exposure to biologics (56.8% [BPAP] vs 1.2% [VOICE] of patients were biological naïve) and several variables that were not available for both studies, as well as potential unmeasured confounders that could not be adjusted through statistical methods may have resulted in biased estimates; this significant difference in the proportion of biologic-naïve patients might indicate potentially different response to benralizumab and response to PSP at the population level. Additionally, for both groups, healthcare professionals may not have reported biologic-naïve status uniformly across patients. The PSP cohort had low data capture rates for variables that may be potential confounders in the analysis, such as baseline maintenance oral corticosteroid use and ACQ-6 scores.

Patients treated with benralizumab in BPAP and VOICE may have been selected based on slightly different criteria: the drug was offered free of charge prior to NHS reimbursement arrangements in the BPAP study while in VOICE study, benralizumab was prescribed following NHS reimbursement criteria. The index date for the PSP group also occurred after some patients had received their first benralizumab injection, and study data did not capture discontinuations occurring before the index date, potentially underestimating the discontinuation rate in this group. Furthermore, treatment discontinuation was strictly defined for the PSP group as a 9-week gap in drug administration, yet discontinuation in the non-PSP group was defined by the treating physician, who may have recorded treatment discontinuation after an administration gap longer or shorter than 9 weeks. Finally, the BPAP study was primarily conducted before the COVID-19 pandemic, whereas the VOICE study started at the beginning of the COVID-19 pandemic. The COVID-19 pandemic altered some physician and patient behaviours, which may have affected the outcomes of PSP participation.

CONCLUSIONS

Participation in PSPs provides benefits in asthma medication adherence and persistence, asthma control, HRQoL and HCRU. Patient education and support regarding asthma therapy administration (for inhalers and injectable biologics) are particularly important in this population, especially in the context of the transition to at-home treatment and remote disease monitoring. Participation in a PSP was associated with lower discontinuation rates for biologics, as exemplified by benralizumab-treated patients with severe asthma who enrolled in the Connect 360 PSP. This effect was seen even after considering prior biological use and a longer duration for discontinuation monitoring.

There is a need for future studies to be more transparent about the components of their PSPs to support comparison across programmes. Research that captures other direct outcomes of treatment (eg, frequency of exacerbations, HRQoL, activities of daily living) with more complete reporting of potential confounders is warranted. Additionally, explorations of cost-effectiveness

would be especially useful in determining the sustainability of PSPs and whether the clinical and quality of life benefits justify the costs to the healthcare system. The findings of this study suggest that PSPs should be strongly considered as ways to improve patient adherence to asthma therapy and control severe asthma.

Author affiliations
[1]AstraZeneca UK Limited, Cambridge, UK
[2]Imperial College London, London, UK
[3]Royal Free NHS Trust, London, UK
[4]Cytel Inc, Waltham, Massachusetts, USA
[5]BMJ Open Respiratory Research, Edinburgh, UK
[6]Centre of Infection and Immunity, Queens University Belfast, Belfast, UK

X Olivia Fulton @just_TUX

Acknowledgements The authors would like to thank Allison Brackley for providing editorial support.

Contributors APJR, DK, TM, WJL, VHS, LO, MGM, ZL, SH, AM and LGH had substantial contributions to study concept and design. Literature searches were performed by MGM and SH; statistical analyses were performed by ZL and LO. APJR, MGM, DK, TM, ZL and LO had substantial contributions to analysis and interpretation of the data. Patient perspective insight was provided and written by OF. All authors contributed to manuscript drafting, critically revised the work and agreed with the presented findings. All authors are responsible for the overall content as guarantors. All authors approved the version of the article to be published.

Funding This study was supported by AstraZeneca (grant number: n/a). AM is supported by the NIHR Applied Research Collaboration NW London. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Competing interests DK and TM are employees of AstraZeneca; APJR and VHS were employees of AstraZeneca at the time the study was conducted; LO is an employee of Cytel contracted by AstraZeneca; MGM, ZL and SH are employees of Cytel who was contracted by AstraZeneca for support in conducting this study; WJL is an external consultant at Wei Medical Consultancy and a medical doctor affiliated with Royal Free NHS Trust; LGH has received grant funding, participated in advisory boards and given lectures at meetings supported by Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Hoffmann la Roche, GlaxoSmithKline, Novartis, Theravance, Evelo Biosciences, Sanofi and Teva; he has received grants from MedImmune, Novartis UK, Roche/Genentech and GlaxoSmithKline, Amgen, Genentech/Hoffman la Roche, AstraZeneca, MedImmune, GlaxoSmithKline, Aerocrine and Vitalograph; he has received sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK and Napp Pharmaceuticals; he has also taken part in asthma clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, Hoffmann la Roche and GlaxoSmithKline for which his institution received remuneration; he is the Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma which involves industrial partnerships with a number of pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffmann la Roche and Janssen.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study did not require approval by an Ethics committee or Institutional Board as it analysed de-identified patient-level data retrospectively collected during participation in the CONNECT 360 patient support programme and BPAP benralizumab patient access programme. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Adrian P J Rabe http://orcid.org/0000-0001-5237-0677
Wei J Loke http://orcid.org/0000-0003-2266-5938

REFERENCES

1 Backman H, Jansson S, Stridsman C, *et al*. Severe asthma—a population study perspective. *Clin Experimental Allergy* 2019;49:819–28.
2 Hekking P-P, Wener RR, Amelink M, *et al*. The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015;135:896–902.
3 Jochmann A, Artusio L, Jamalzadeh A, *et al*. Electronic monitoring of adherence to inhaled corticosteroids: an essential tool in identifying severe asthma in children. *Eur Respir J* 2017;50.
4 Wang G, Wang F, Gibson PG, *et al*. Severe and uncontrolled asthma in China: a cross-sectional survey from the Australasian severe asthma network. *J Thorac Dis* 2017;9:1333–44.
5 Chung KF, Wenzel SE, Brozek JL, *et al*. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343–73.
6 Charles D, Shanley J, Temple SN, *et al*. Real-world efficacy of treatment with Benralizumab, Dupilumab, Mepolizumab and Reslizumab for severe asthma: a systematic review and meta-analysis. *Clin Exp Allergy* 2022;52:616–27.
7 Dragonieri S, Carpagnano GE. Biological therapy for severe asthma. *Asthma Res Pract* 2021;7:12.
8 Leonard SI, Turi ER, Powell JS, *et al*. Associations of asthma self-management and mental health in adolescents: a scoping review. *Respiratory Medicine* 2022;200:106897.
9 Ji Z, López-de-Andrés A, Jiménez-García R, *et al*. Mental health in patients with asthma: a population-based case-control study. *Respiratory Medicine* 2022;193.
10 Bårnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. *Respir Care* 2015;60:455–68.
11 Sulaiman I, Greene G, MacHale E, *et al*. A randomised clinical trial of feedback on Inhaler adherence and technique in patients with severe uncontrolled asthma. *Eur Respir J* 2018;51:1701126.
12 Ganguli A, Clewell J, Shillington AC. The impact of patient support programs on adherence, clinical, humanistic, and economic patient outcomes: a targeted systematic review. *Patient Prefer Adherence* 2016;10:711–25.
13 Rabe AP, Loke WJ, Heaney LG, *et al*. Pcr20 diversity of patient support programs for severe asthma treated with biologic therapies – a systematic literature review. *Value in Health* 2022;25.
14 Sacristán JA, Artime E, Díaz-Cerezo S, *et al*. The impact of patient support programs in Europe: a systematic literature review. *Patient* 2022;15:641–54.
15 Fendrick AM, Brixner D, Rubin DT, *et al*. Sustained long-term benefits of patient support program participation in immune-mediated diseases: improved medication-taking behavior and lower risk of a hospital visit. *JMCP* 2021;27:1086–95.
16 Ryan C, Calimlim B, Lucas J. Assessing the impact of patient support programs on patient outcomes in adalimumab-treated patients with psoriasis in Europe. JAAD 2018;79.
17 Morris T, Ali S, Hunt J, *et al*. Characteristics and outcomes of patients with severe eosinophilic asthma treated with Benralizumab enrolled in the connect 360 patient support programme in the UK. In: Morris T, Ali S, hunt J, eds. American Thoracic Society 2022 International Conference, May 13-18, 2022 - San Francisco, CA; May 2022
18 Jackson D, Dube S, Morris T, *et al*. Improvement of clinical outcomes in severe eosinophilic asthma patients treated with Benralizumab in real-world clinical practice in England: XALOC study programme. American Thoracic Society 2020 International Conference, May 15-20, 2020 - Philadelphia, PA; May 2020:A3028–A.
19 Chiu CJ, Huang MT. Asthma in the precision medicine era: biologics and probiotics. *Int J Mol Sci* 2021;22:4528.
20 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:71.

21 Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in Healthcare. 2009.
22 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343.
23 National Institute for Health and Care Excellence (NICE). NICE DSU technical support document number 7: evidence synthesis of treatment efficacy in decision making: A reviewer's checklist. 2012.
24 GA Wells BS, O'Connell D, Peterson J, *et al*. The Newcastle-Ottawa scale (NOS) for assessing the quality of Nonrandomised studies in meta-analyses. n.d. Available: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
25 Brandenberger J, Tylleskär T, Sontag K, *et al*. A systematic literature review of reported challenges in health care delivery to migrants and refugees in high-income countries - the 3C model. *BMC Public Health* 2019;19:755.
26 National Institute for Health and Care Excellence (NICE). Benralizumab for treating severe eosinophilic asthma. NICE; 2019.
27 AstraZeneca. Benralizumab Smpc. 2018.
28 Jackson DJ, Burhan H, Menzies-Gow A, *et al*. Benralizumab effectiveness in severe asthma is independent of previous biologic use. *J Allergy Clin Immunol Pract* 2022;10:1534–44.
29 National Institute for Health and Care Excellence (NICE). NICE guideline [Ng166] retraction. 2022 Available: https://www.nice.org.uk/guidance/ng166?UID=70579609202227250l9
30 National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: severe asthma (Ng166). 2020.
31 Makhecha S, Jamalzadeh A, Irving S, *et al*. Paediatric severe asthma Biologics service: from hospital to home. *Arch Dis Child* 2021;106:900–2.
32 Elsey L, Holmes LJ, Johnson K, *et al*. P91 A review of severe asthma patients' adherence to preventer Inhalers after 12 months of Mepolizumab. British Thoracic Society Winter Meeting 2019, QEII Centre, Broad Sanctuary, Westminster, London SW1P 3EE, 4 to 6 December 2019, Programme and Abstracts; 2019:A139–40.
33 Estrada JI, Restrepo AM, Giraldo PA, *et al*. Drug-safety program impact at health related quality of life at patients diagnosed with persistent severe asthma. *Value in Health* 2017;20.
34 Estrada JI, Restrepo AM, Giraldo PA, *et al*. Drug-safety program impact in hospitalization persistent severe asthma patients. *Value in Health* 2017;20.
35 Estrada JI, Restrepo AM, Giraldo PA, *et al*. Drug-safety program impact at health care perception at patients diagnosed with persistent severe asthma. *Value in Health* 2017;20.
36 Estrada JI, Restrepo AM, Giraldo PA, *et al*. Drug-safety program impact in the emergency frequency at patients with persistent severe asthma. *Value in Health* 2017;20.
37 Benfante A, Principe S, Cicero MN, *et al*. Management of severe asthma during the first lockdown phase of SARS-Cov-2 pandemic: tips for facing the second wave. *Pulm Pharmacol Ther* 2022;73–4.
38 Fui A, Fini D, Sivori M. Self-administration of biologic therapy in severe asthma and chronic Rhinosinusitis with nasal polyps: compliance and quality of life improvement. *CHEST* 2022;161.
39 Cohn L, Zhang Y, Wang J, *et al*. Real-world effectiveness of dupilumab on patient-reported outcomes and symptoms in asthma: 3-month follow-up data from RESPIRE, an observational study with patients recruited from a US Dupilumab patient support program. *Chest* 2021;160:A29–30.
40 d'Ancona G, Bains S, Stewart-Kelcher N, *et al*. P104 does asthma control change following transition to home Benralizumab administration? British Thoracic Society Winter Meeting, Wednesday 17 to Friday 19 February 2021, Programme and Abstracts; 2021
41 d'Ancona G, Stewart-Kelcher N, Bains S, *et al*. P105 Does asthma control change when patients transition to home administration of mepolizumab? British Thoracic Society Winter Meeting, Wednesday 17 to Friday 19 February 2021, Programme and Abstracts; February 2021:A144–5.
42 Liebhaber M, Dyer Z. Home therapy with subcutaneous anti-immunoglobulin-E antibody omalizumab in 25 patients with immunoglobulin-E-mediated (allergic) asthma. *J Asthma* 2007;44:195–6.
43 Namazova-Baranova L, Vishneva E, Smirnov V, *et al*. The opport unities of internet technology and telemedicine in interaction between doctor and patient. *Value in Health* 2015;18.
44 Reed N, Bird T, Peters M, *et al*. Evaluating the process of transitioning patients care from the hospital to general practice. *Respirology* 2019;24.
45 Bègne C, Justet A, Dupin C, *et al*. Evaluation in a severe asthma expert center improves asthma outcomes regardless of step-up in asthma therapy. *J Allergy Clin Immunol Pract* 2020;8:1439–42.
46 Allen DJ, Holmes LJ, Hince KA, *et al*. Nonadherence with inhaled preventer therapy in severe asthmatic patients on long-term omalizumab. *Eur Respir J* 2018;52:1801025.
47 McCallum GB, Morris PS, Brown N, *et al*. Culture-specific programs for children and adults from minority groups who have asthma. *Cochrane Database Syst Rev* 2017;8.
48 Abbas H, Yehya L, Kurdi M, *et al*. Patients' knowledge and awareness about patient support programs: a cross-sectional study on lebanese adults with chronic diseases. *Int J Technol Assess Health Care* 2021;37:e34.
49 Stack RJ, Bundy CE, Elliott RA, *et al*. Intentional and unintentional non-adherence in community dwelling people with type 2 diabetes: the effect of varying numbers of medicines. *Diabetes & Vascular Disease* 2010;10:148–52.
50 Abbaspur-Behbahani S, Monaghesh E, Hajizadeh A, *et al*. Application of mobile health to support the elderly during the COVID-19 outbreak: a systematic review. *Health Policy Technol* 2022;11:100595.
51 Behar JA, Liu C, Kotzen K, *et al*. Remote health diagnosis and monitoring in the time of COVID-19. *Physiol Meas* 2020;41.
52 Giubergia V, Ramirez Farias MJ, Perez V, *et al*. Clinical impact of omalizumab treatment in children with severe asthma: report of a local experience. impacto clinico del tratamiento con omalizumab en ninos con asma grave: reporte de una experiencia local. 2019;117:e115–20.
53 Giubergia V, Ramirez Farías MJ, Pérez V, *et al*. Severe asthma in pediatrics: outcomes of the implementation of a special health care protocol. *Arch Argent Pediatr* 2018;116:105–11.
54 Al-Jahdali HH, Khan M, AL-Harbi A, *et al*. Severe asthma patients experience and satisfaction with virtual clinics in a large tertiary care hospital during COVID-19 period. American Thoracic Society 2021 International Conference, May 14-19, 2021 - San Diego, CA; 2021
55 Hansen S, Hilberg O, Ulrik CS, *et al*. The Danish severe asthma register: an electronic platform for severe asthma management and research. ECRJ 2021;8:1842117.
56 Guarnieri G, Caminati M, Achille A, *et al*. Severe asthma, telemedicine, and self-administered therapy: listening first to the patient. *J Clin Med* 2022;11:960.
57 Timmermann H, Mailänder C. Home self-administration of biologics - a German survey among Omalizumab-treated patients with severe asthma and their treating physicians. *Pneumologie* 2020;74:103–11.
58 Flokstra-de Blok B, Kocks J, Wouters H, *et al*. Perceptions on home-administration of biologics in the context of severe asthma: an international qualitative study. *J Allergy Clin Immunol Pract* 2022;10:2312–23.
59 Rodrigues Sousa S, Tenda A, Farinha I, *et al*. Home administration of biological treatment in severe asthma in real-life experience: impact on asthma control and quality of life. *Eur Ann Allergy Clin Immunol* 2023;55:35–40.
60 Bendien SA, van Leeuwen MM, Lau HS, *et al*. Home-based intravenous treatment with reslizumab for severe asthma in the Netherlands - an evaluation. *Respiratory Medicine* 2022;194:106776.