PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The perspectives of mild asthma patients on maintenance versus as-needed preventer treatment regimens: a qualitative study
AUTHORS	Foster, Juliet; Beasley, Richard; Braithwaite, Irene; Harrison, Tim; Holliday, Mark; Pavord, Ian; Reddel, Helen

VERSION 1 – REVIEW

REVIEWER	Mroueh, Salman American University of Beirut, Pediatrics and Adolescent Medicine
REVIEW RETURNED	25-Feb-2021

GENERAL COMMENTS	This study addresses a timely issue brought about by the recent GINA recommendations of using an as needed combined inhaled corticosteroid and beta agonist for the symptomatic management of mild asthma. It affirms some already known facts (the importance of patient education in this population...) and confirms some intuitive others (why would patients take a medicine when they are fine, especially if it does not help when they have symptoms?). While most patients preferred the as needed combination treatment, despite some reservations (does not relieve fast enough, probably more expensive?), did any of the patients appreciate that it provided longer relief?

REVIEWER	Sheehan, William Children's National Health System, Allergy and Immunology
REVIEW RETURNED	01-Mar-2021

GENERAL COMMENTS	The authors present a qualitative study on the experiences and future treatment preferences of mild asthma patients who were enrolled in a study comparing "maintenance" therapy (budesonide BID + salbutamol PRN) to "as needed" therapy (PRN use of combination budesonide-formoterol). To do this, they invited a subset of 108 participants from the NovelSTART RCT with 74 of those participants completing the interview for this presented analysis. The study and interviews revealed key trends in patient perspectives regarding their motivation in dealing with mild asthma. These trends are outlined in the manuscript and include perceived asthma burden (generally considered to be low by the participants), knowledge of their disease, and beliefs about the benefits/risks of their treatment options. The manuscript highlights direct quotes from participants regarding these these topics. The Results then close with the authors noting personal preference of

	asthma treatment - most interviewees, within both RCT groups, preferred the “as needed” therapy for future treatment. The importance of this research is to provide physicians with a better understanding of patient perspectives on their own asthma disease and their asthma therapy choices. This may facilitate an improved physician-patient relationship leading to improved personalized asthma treatment choices resulting in reduced asthma morbidity. Major Comment 1. The authors note in the abstract, results, and discussion that the simplicity of the “as needed” treatment choices was preferred by “most participants” in both arms of the RCT. The reader does not know what is meant by “most.” I do not understand why they do not present the exact numbers? It seems this would have greatly strengthened the manuscript. What percentage of the 39 interviewees in the “maintenance” group and what percentage of the 35 interviewees in the “as-needed” group preferred the “as needed” option? Were there preference differences between the two groups? Minor Comments 1. 108 participants were invited (74 completed interview) for this substudy. What percentage of the entire population of the NovelSTART RCT did this represent? How representative of the overall NovelSTART study were these 108 (74) participants? I assume they were representative by age and sex (manuscript Methods notes this). Were they also representative by education and geography? I am getting at the question of if these 108 were selected for any specific reason (i.e. ease of location close to NOVELQ team). 2. 108 participants were invited for this substudy with 79 finally completing the interview (39 in “maintenance” group and 35 in “as needed” group. However, it was never noted how many from each arm were in the initial 108 invited participants? I assume approximately 54 in each group, but wanted the authors to clarify in the manuscript. This is to make sure there was not a significant difference between the two groups in regards to agreeing to be interviewed for this substudy.

REVIEWER	Searle, Aidan National Institute for Health Research (NIHR) Biomedical Research Unit in Nutrition, Diet and Lifestyle at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol, Bristol Biomedical Research Centre
REVIEW RETURNED	29-Apr-2021

GENERAL COMMENTS	This is a well conducted and presented qualitative evaluation of the perspectives of asthma patients' treatment regimens in the context of a clinical trial. There are a number of issues that need clarification and some issues are worthy of further discussion. Firstly, a broader concern is to what extent participation in the trial influenced adherence to treatment following the 10-month period

	of open label treatment? Related to this did the authors consider participants' general beliefs / perceptions of asthma about the condition and its treatment - their affect on relationship with treatment preferences and implications for a patient-centered approach to care (i.e, Horne et al). More specifically, the design of this qualitative work appears very pragmatic and deductive although the authors report taking an inductive approach. Firstly, it was not clear how coding of transcripts was conducted and how consensus of coding was achieved as only JMF identified as coder. Although this author was not a clinician or involved in clinical trial a reflexivity statement would be desirable. Which authors were involved with development of topic guide and what was the crossover with design of the clinical trial? Can you give an example of a revision made to the topic guide? The topic guide comprises of relatively closed questions and appear closely related to the the way the findings are presented again suggesting a more deductive approach? I hope these issues can be addressed in the analysis and discussion sections before consideration for publication.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Dr. Salman Mroueh

This study addresses a timely issue brought about by the recent GINA recommendations of using an as needed combined inhaled corticosteroid and beta agonist for the symptomatic management of mild asthma. It affirms some already known facts (the importance of patient education in this population...) and confirms some intuitive others (why would patients take a medicine when they are fine, especially if it does not help when they have symptoms?):

Thank you for your positive comments on this study. We agree that intuitive knowledge is useful in clinical care and that it is important to add robust research to intuitive assumptions in order to ensure appropriate evidence-based patient care.

R1.1.

While most patients preferred the as needed combination treatment, despite some reservations (does not relieve fast enough, probably more expensive?), did any of the patients appreciate that it provided longer relief?

A1.1. Although participants did not use the term “longer relief”, participants in both RCT randomisation groups articulated this outcome as having noticeably less asthma symptoms and/or needing relief treatment less often.

To make clarify this finding of perceived longer relief, we have amended text in section 3.1.4.: “Though many interviewees found their randomised treatment regimen effective (e.g. perceiving longer relief, *i.e.* feeling less wheezy, needing to use their reliever less)…”

The reviewer may be interested that although the upfront cost of the ICS-formoterol may be higher than the upfront cost of ICS alone, the as-needed treatment was taken on average only 3-4 doses per week in the RCTs, so the average cost for the patient may be less. From a UK payer perspective, as-

needed ICS-formoterol is more cost-effective than regular ICS (FitzGerald et al, Respiratory Medicine 171 (2020) 106079[1]).

Reviewer #2 Dr. William Sheehan

The authors present a qualitative study on the experiences and future treatment preferences of mild asthma patients who were enrolled in a study comparing "maintenance" therapy (budesonide BID + salbutamol PRN) to "as needed" therapy (PRN use of combination budesonide-formoterol). To do this, they invited a subset of 108 participants from the NovelSTART RCT with 74 of those participants completing the interview for this presented analysis.

The study and interviews revealed key trends in patient perspectives regarding their motivation in dealing with mild asthma. These trends are outlined in the manuscript and include perceived asthma burden (generally considered to be low by the participants), knowledge of their disease, and beliefs about the benefits/risks of their treatment options. The manuscript highlights direct quotes from participants regarding these topics. The Results then close with the authors noting personal preference of asthma treatment - most interviewees, within both RCT groups, preferred the "as needed" therapy for future treatment.

The importance of this research is to provide physicians with a better understanding of patient perspectives on their own asthma disease and their asthma therapy choices. This may facilitate an improved physician-patient relationship leading to improved personalized asthma treatment choices resulting in reduced asthma morbidity.

Thank you for this positive summary of the study.

R2.1. *Major Comment*. The authors note in the abstract, results, and discussion that the simplicity of the "as needed" treatment choices was preferred by "most participants" in both arms of the RCT. The reader does not know what is meant by "most." I do not understand why they do not present the exact numbers? It seems this would have greatly strengthened the manuscript. What percentage of the 39 interviewees in the "maintenance" group and what percentage of the 35 interviewees in the "as-needed" group preferred the "as needed" option?

A2.1. We appreciate this comment. Qualitative research aims to collect rich data about "how" and "why" in a small sample size selected to represent the range of participant diversity, as opposed to quantitative research where questions of "to what extent" and "when" are answered in a large population representative sample. Although there is a lively debate on quantification in qualitative research, particularly with respect to mixed methods studies,[2] quantification in qualitative research is usually limited to "quasi-statistical" terms such as "some," "most" etc. in order to avoid inferring greater generality than is justified for the study design and results. This principle cautions against the systematic statement of frequency counts through our paper. However, as argued by Weiss (1994)[3] proportions may be reported when an issue is central to a study. Given the reviewer's request on this central topic we have added the following on page 11.

"Most interviewees, within both RCT groups, preferred a single combined inhaler over a separate reliever and preventer inhaler for their future treatment (77% in "as-needed"; 64% in "maintenance" group).

2. Were there preference differences between the two groups?

A2.2. Yes the preference differences between the two groups are reported in the manuscript. We have amended the text in various manuscript locations to make it clearer where preferences converge or differ e.g.:

"Interviewees*, within both RCT groups,* considered a combined inhaler easier to manage (e.g. one thing to remember to carry); as requiring less prescriptions and lower costs; and as providing a physical feeling of relief …" (section 3.2.1.)

"*Only* 'Maintenance regimen' interviewees felt that a combination inhaler may cause unnecessary use or overuse of preventer medication" (section 3.2.2.)

Also, the following note has been added under table VI:

"* Note: For a given rationale, if a quotation is tabulated for only one RCT group, that rationale only emerged in the single RCT group named"

R2.3.1 108 participants were invited (74 completed interview) for this substudy. What percentage of the entire population of the NovelSTART RCT did this represent?

A2.3.1.

The following text has been added to the supplementary material (pg. 6):

"The 108 total participants invited represented 24.3% of the total NovelSTART RCT patients in these randomisation groups (n=225 Maintenance; n=220 in "As needed combination"). *Of those invited* n=14 (13%) expressed initial interest… Seventy four (68.5%) *of invited* participants were interviewed, 39 (53%) in the Maintenance group, and 35 (47%) in the As-needed combination group. These 74 interviewees represented 16.6% of the total NovelSTART RCT patients in these randomisation groups. Participants were selected by purposive sampling to provide diversity by age and sex, and interviews were continued until data saturation was achieved.

R2.3.2 How representative of the overall NovelSTART study were these 108 (74) participants? I assume they were representative by age and sex (manuscript Methods notes this). Were they also representative by education and geography? I am getting at the question of if these 108 were selected for any specific reason (i.e. ease of location close to NOVELQ team).

A2.3.2. Patients were selected by the qualitative team using a de-identified database. Since interviews were conducted by telephone, locality/geography or other convenience factors were not included in the selection process. The NovelQ study sample was similar to the NovelSTART sample on demographic e.g. age and gender, and clinical factors e.g. FEV1% predicted and ACQ score.

As above, participants were selected by purposive sampling to provide diversity by age and sex, and interviews were continued until data saturation was achieved.

R2.4. 108 participants were invited for this substudy with 79 finally completing the interview (39 in "maintenance" group and 35 in "as needed" group. However, it was never noted how many from each arm were in the initial 108 invited participants? I assume approximately 54 in each group, but wanted the authors to clarify in the manuscript. This is to make sure there was not a significant difference between the two groups in regards to agreeing to be interviewed for this substudy.

A2.4. Thank you for this question. Of those invited, a smaller proportion from the As-needed group agreed to be interviewed, so it is possible that those who consented may have had a more positive attitude to the treatment. However, we note that the overall preferences for a combination inhaler (77% of "as-needed" group; 64% of "maintenance" group) expressed during these qualitative interviews are similar to the preferences reported from a quantitative survey conducted at the end of the PRACTICAL study (Baggott et al, Eur Respir J 2020; 55: 1902073).[4]

In response to the reviewer's question, we have amended the results section as follows:

"Of 108 participants invited, *39 of 50 (78%) in the Maintenance group and 35 of 58 (60%) "As-needed" group participated in an interview* (supplementary material)."

In addition, in the Discussion on limitations of the study, we have added the following (page 16):

*"*A smaller proportion of RCT participants invited from the "As-needed" group agreed to be interviewed, so those who consented to interview may have had a more positive view towards this treatment.*"*

Reviewer 3 Dr. Aidan Searle

This is a well conducted and presented qualitative evaluation of the perspectives of asthma patients' treatment regimens in the context of a clinical trial. There are a number of issues that need clarification and some issues are worthy of further discussion… I hope these issues can be addressed in the analysis and discussion sections before consideration for publication.

Thank you for the positive comments about this study.

R3.1.1.

Firstly, a broader concern is to what extent participation in the trial influenced adherence to treatment following the 10-month period of open label treatment?

R3.1.1. Thank you for raising this. During the interviews, we explored what choice patients would make if they were offered these treatments in the future. Since the interviews were conducted before the patients had completed the clinical trial, and before as-needed budesonide-formoterol had been approved for use in clinical practice, we do not have any information about what treatment(s) the interviewees were offered by their own doctors after the end of the study, and what their adherence might have been if they were prescribed maintenance ICS. However data from other studies indicate that treatment adherence is likely to be higher in RCT participants than in the community, and for patients randomised in this study to maintenance ICS, better adherence could have provided a better clinical response during the study than would normally be seen in the broader community.

We have added a comment about this in the limitations section of the discussion as follows:

"Limitations include that interviewees were participants in a 12-month long RCT (which for those prescribed maintenance ICS may have increased their treatment adherence during the study), and had been receiving …thus limiting the generalizability of the results to patients in the general community"

R3.1.2. Related to this did the authors consider participants' general beliefs / perceptions of asthma about the condition and its treatment - their affect on relationship with treatment preferences and implications for a patient-centered approach to care (i.e, Horne et al).?

A3.1.2. This study used an inductive approach to identify emergent beliefs and asthma perceptions, and explore their relationship with treatment preferences. As we report in the manuscript, depending on the regimen, the drivers of treatment preference (reported in the section 3.2 and table VI) included pragmatic (convenience, cost) behavioural (rewards that support adherence e.g. physical sensation of relief), and treatment (effectiveness and familiarity) factors. Broader beliefs and perceptions did emerge in the data (e.g. feeling that mild asthma only required minimal treatment [pg. 8], perceiving uncontrolled asthma versus controlled asthma [pg. 8] and concern about side effects [pg. 11]) but these showed no clear relationship with treatment preference in our data.

A future deductive qualitative study focussing on if and how different components of a behavioural model (such as the necessity-concerns framework) affect treatment preferences and impact patient care would be a useful addition to the small existing literature. We have added the following text in the manuscript, including a systematic review from Horne and colleagues[5], to address this important point:

"Further, future research investigating the extent to which components of behavioural models (e.g. the necessity-concerns framework)[5] influence treatment preferences and impact patient care in mild asthma would be a very useful next step to enhance the literature on patient choices and acceptance of regimen options for mild asthma."

R3.2.1. More specifically, the design of this qualitative work appears very pragmatic and deductive although the authors report taking an inductive approach….The topic guide comprises of relatively closed questions and appear closely related to the the way the findings are presented again suggesting a more deductive approach?

A3.2.1. Although our interview guide included some primary questions that were rather pragmatic, our secondary questions were open and explorative (e.g. How do you feel about this medication?; What made the difference between you using your inhaler or not?; What made you choose that answer?) and allowed for an inductive approach. Evidence for this is shown by the emergence of rich data during the interviews, especially around life with asthma and the wide range of rationales for treatment preference encompassing ease of use, adherence support and perceived treatment effectiveness.

R3.2.2 Firstly, it was not clear how coding of transcripts was conducted and how consensus of coding was achieved as only JMF identified as coder. Although this author was not a clinician or involved in clinical trial a reflexivity statement would be desirable

R3.2.2. A reflexivity statement has been added to the supplementary material (pg. 5) and includes the following section on 'Team involvement and coding reliability':

Team involvement and coding reliability

Data were coded by co-author JMF. At significant points during the process of data analysis including the later stages of the analysis, JMF (who collected the data and undertook the analysis, but had no involvement in the main RCT) and HKR (with extensive clinical and treatment knowledge and key involvement in the RCT) read new transcripts and/or met to discuss emerging codes and categories, the interpretation of these and potential new lines of enquiry. Overall themes were discussed throughout data collection and analysis with healthcare professional colleagues not involved in the RCT.

R3.3.1

Which authors were involved with development of topic guide and what was the crossover with design of the clinical trial?

A3.3.1. The qualitative research was prospectively embedded within the RCT in order to understand patient experience and perspectives of the new therapeutic regimen and of the regular treatment previously recommended for mild asthma [protocol publication: Beasley et al, Eur Respir J 2016; 47: 981–984)[6]. The interview guide was developed after the RCT protocol was finalised, so that terms used in the interview guide would align with features such as the colour of study inhalers, but before any study results were known by any of the investigators.

We have added the following text on page 4 of the supplementary material:

"The interview guide was developed by co-authors JMF and HKR, and then provided to all other authors for their feedback prior to the start of recruitment."

R3.3.2

Can you give an example of a revision made to the topic guide?

A3.3.2. We have added the following text on page 4 of the supplementary material:

"Only minor changes to the guide layout were required (e.g. we changed the order of some questions to improve the flow of the interviews)…"

Please see the footnote of the interview guide in the supplementary material which describes the two questions that were added to the interview guide after interview 5. (i.e. "Questions 5 and 7 were added after the 5th interview to more deeply explore patient-perceived treatment priorities and preferences, and were asked only if time allowed so not all interviewees answered them")

REFERENCES

1. FitzGerald JM, Arnetorp S, Smare C, et al. The cost-effectiveness of as-needed budesonide/formoterol versus low-dose inhaled corticosteroid maintenance therapy in patients with mild asthma in the UK. Respir Med. 2020; 171: 106079. DOI: 10.1016/j.rmed.2020.106079.

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3. Weiss, R. S. (1994). Learning from strangers: The art and method of qualitative interviewing. New York: The Free Press.

4. Baggott C, Reddel HK, Hardy J, et al. Patient preferences for symptom-driven or regular preventer treatment in mild to moderate asthma: findings from the PRACTICAL study, a randomised clinical trial. ERJ. 2020; 55: 1902073; DOI: 10.1183/13993003.02073-2019

5. Horne R, Chapman SC, Parham R, et al. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. PLoS One. 2013; 8: e80633. doi: 10.1371/journal.pone.0080633.

6. Beasley R, Pavord I, Papi A, et al. Description of a randomised controlled trial of inhaled corticosteroid/fast-onset LABA reliever therapy in mild asthma. Eur Respir J 2016;47:981-984.

VERSION 2 – REVIEW

REVIEWER	Searle, Aidan National Institute for Health Research (NIHR) Biomedical Research Unit in Nutrition, Diet and Lifestyle at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol, Bristol Biomedical Research Centre
REVIEW RETURNED	14-Jul-2021

GENERAL COMMENTS	I am satisfied that the comments from both sets of reviewers have been addressed and have raised the quality such that the manuscript is now acceptable for publication in BMJ Open.