RESEARCH ARTICLE

REVISED A grumbling concern: A survey of gastrointestinal symptoms in cystic fibrosis in the modulator era [version 2; peer review: 2 approved, 3 approved with reservations]

Previous Title 'A grumbling concern: an international survey of gastrointestinal symptoms in cystic fibrosis in the modulator era'

Rebecca J Calthorpe[1], Natalie Goodchild[2], Vigilius Gleetus[1], Vinishaa Premakumar[1], Bu Hayee[3], Zoe Elliott[2], Bethinn Evans[2], Nicola J Rowbotham[1], Siobhán B Carr[4], Helen Barr[1,5], Alexander Horsley[6], Daniel Peckham[7], Alan R Smyth[1]

[1]University of Nottingham School of Medicine & NIHR Nottingham Biomedical Research Centre, Nottingham, UK
[2]Patient and Public representative, N/A, UK
[3]Kings College Hospital NHS Foundation Trust, London, UK
[4]Royal Brompton Hospital (part of GSTT) and Imperial College, London, UK
[5]Nottingham University Hospitals NHS Trust, Nottingham, UK
[6]University of Manchester & NIHR Manchester Biomedical Research Centre, Manchester, UK
[7]Leeds Institute of Medical Research at St James's, Leeds, UK

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Abstract

Background

Gastrointestinal symptoms in cystic fibrosis (CF) are common and intrusive to daily life. Relieving gastrointestinal symptoms was identified as an important research priority and previously explored in an international survey in 2018. However, following the widespread introduction of cystic fibrosis transmembrane conductance regulator (CFTR) modulators in 2019, the landscape of CF treatment has changed. We repeated an online survey to further describe gastrointestinal symptoms and their effect on quality of life (QoL) in the CFTR modulator era.

Methods

An electronic survey consisting of closed questions and free text

Open Peer Review

Approval Status ✓ ? ✓ ? ?

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version 2 (revision) 05 Feb 2024			✓ view		
version 1 14 Apr 2023	✓ view	? view	? view	? view	? view

1. **Dhiren Patel**, Saint Louis University, St. Louis, USA
2. **Mette Frahm Olsen**, University of Copenhagen, Copenhagen, Denmark
3. **Drucy Borowitz**, University at Buffalo, Buffalo, USA

responses was distributed via social media and professional networks for a period of one month between March - April 2022. People with CF (pwCF), their family and friends, and healthcare professionals (HCPs) were invited to take part.

Results

There were 164 respondents: 88 pwCF (54%), 22 (13%) family, and 54 (33%) healthcare professionals (HCPs). A total of 89/110 (81%) pwCF or family members reported CFTR modulator treatment. The most commonly reported symptoms were wind / gas and rumbling stomach noises (borborygmi) in both the modulator and non-modulator groups in addition to loose motions (modulator group) and bloating (no modulator group). Abdominal pain and bloating had the greatest impact on QoL.

For those on a CFTR modulator, the proportion of pwCF reporting “no change” or “worse” for all of the symptoms surveyed was greater than the proportion reporting an improvement. For some symptoms such as stomach pains and reduced appetite, improvements were perceived more commonly in HCPs than what was reported by pwCF. Following modulator introduction, dietary changes to manage GI symptoms were recommended by 28/35 (80%) of HCPs and reported by 38/76 (50%) lay respondents. Changes in medication were recommended by 19/35 (54%) HCPs and reported by 44/76 (58%) of patients and family members.

Conclusion

This survey has shown that gastrointestinal symptoms remain prevalent in pwCF in the CFTR modulator era, though the nature of these symptoms may have changed. A better understanding of the underlying pathophysiology of these symptoms is essential. Future clinical studies should focus on improving symptoms and QoL.

Plain language summary

What is already known: Gastrointestinal symptoms are common and intrusive to everyday life for people with cystic fibrosis (CF), however the majority of studies reporting gastrointestinal symptoms in CF are published prior to the widespread introduction of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies. These are medications which target the underlying defect in CF rather than the consequences of CFTR failure.

What this study adds: Through this survey, we describe the similarities and differences of gastrointestinal symptoms for people with CF on modulator therapy compared to those not receiving modulators. Comparisons were also made to our previous work which was completed in 2018 prior to the licensing of the newest and most

4. **Dana Albon**, UVA, Virginia, USA
5. **Barbara Ruaro**, University Hospital of Cattinara, Trieste, Italy

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widely used modulator Elexacaftor / Tezacaftor / Ivacaftor (ETI).

How this study might affect future research: This survey provides a snapshot into gastrointestinal symptoms for people with CF which will be of benefit for researchers as well as clinicians caring for people with CF. Future research into the effects of CFTR modualtors should focus on gastrointestinal symptoms and quality of life. These results will also inform the development of a CF-specific gastrointestinal patient reported outcome measure for people with CF that can be used in clinical trials.

Keywords
Respiratory, cystic fibrosis, gastrointestinal symptoms, CFTR modulators

Corresponding author: Alan R Smyth (alan.smyth@nottingham.ac.uk)

Author roles: Calthorpe RJ: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Goodchild N**: Writing – Review & Editing; **Gleetus V**: Formal Analysis, Writing – Review & Editing; **Premakumar V**: Formal Analysis, Writing – Review & Editing; **Hayee B**: Writing – Review & Editing; **Elliott Z**: Writing – Review & Editing; **Evans B**: Writing – Review & Editing; **Rowbotham NJ**: Methodology, Writing – Review & Editing; **Carr SB**: Writing – Review & Editing; **Barr H**: Writing – Review & Editing; **Horsley A**: Writing – Review & Editing; **Peckham D**: Writing – Review & Editing; **Smyth AR**: Conceptualization, Funding Acquisition, Methodology, Supervision, Writing – Review & Editing

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REVISED **Amendments from Version 1**

The following changes have been after peer review. Abstract: The results include the following sentence "For some symptoms such as stomach pains and reduced appetite, improvements were perceived more commonly in HCPs than what was reported by pwCF".

Manuscript: Within the results, a sentence was added to clarify that all questions were optional with varying completion of the questions and free text responses and that this accounted for the change in denominator for each question. The paragraph relating to symptoms experienced/ reported to healthcare professionals (HCPs) in the diet and medication changes section of the results was removed.

Within the discussion, a paragraph has been added discussing the discrepancies between pwCF and HCP's experiences of GI symptoms and a recommendation for clinicians to be mindful of this and use a CF-specific patient reported outcome measure to objectively assess their patient's experiences of GI symptoms in practice. A paragraph was added discussing notable results, i.e. lack of appetite/ feeling full. The limitation section has been expanded to also include differing denominators for each question due to incomplete survey completion, lack of a standardised population between the two surveys and the small number of responses in the non-modulator group. Additionally, the selection bias section has been expanded to also include risk of not detecting improvements as those with resolved symptoms are less likely to answer the survey. Finally, reference to "international" was removed from the title and manuscript and the limitation section updated to include that although responses were received from multiple countries, the majority were from the UK.

Figures: Legend to Figure 1 updated to clarify labelling of x axis. Figure 2: Denominators added to Figure 2a and 2c. Denominators and survey years included in Figure 2b legend. Title to Figure 3b changed. Figure 4 has been removed.

Any further responses from the reviewers can be found at the end of the article

Introduction

Cystic fibrosis (CF) is an autosomal recessive, life-limiting condition affecting approximately 100,000 people worldwide, caused by mutations to the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein[1] [Cystic Fibrosis FAQs - What is cystic fibrosis?]. It is a chronic multi-system disorder with the gastrointestinal tract being an important cause of morbidity for people with CF (pwCF). Common gastrointestinal symptoms include abdominal pain, flatulence, bloating, and foul-smelling stools[2,3], with over one in five pwCF reporting moderate to severe gastrointestinal symptoms[4]. Approximately 85% of pwCF are pancreatic insufficient necessitating the need for pancreatic enzyme replacement therapy (PERT) and between 2–5% each year will develop distal intestinal obstruction syndrome (DIOS)[5,6].

One of the most important research priorities identified by the CF community in the first James Lind Alliance Priority Setting Partnership (JLA PSP), published in 2018, was 'How can we relieve gastrointestinal symptoms such as stomach pain, bloating and nausea?'[7]. This remained a priority for research in the recent JLA PSP refresh of priorities in 2022, described below. This research question was further explored in 2018 using an online survey involving pwCF, their family and friends, and healthcare professionals (HCPs)[3]. The survey identified the high prevalence of gastrointestinal symptoms in pwCF and negative impact on quality of life, with two thirds of respondents reporting missing school or work due to significant gastrointestinal symptoms[3]. At this time, modulator therapy was only licenced and available for a minority of pwCF with specific genotypes, such as those with a gating mutation or those homozygous for the Phe508del CFTR mutation[8].

More recently, the widespread introduction of the CFTR modulator combination of Elexacaftor / Tezacaftor / Ivacaftor (ETI) (Kaftrio® / Trikafta®, Vertex Pharmaceuticals) in 2019 has changed the landscape of CF treatment. ETI has led to dramatic improvements in respiratory health for patients, including improvements in lung function, reduced pulmonary exacerbations and improved CFQ-R respiratory domain scores, indicating improved quality of life[1,9–11]. The impact of ETI on the gastrointestinal tract is not as well characterised. Early reports suggest some improvement in gastrointestinal symptoms after initiation of ETI therapy[12]. This was demonstrated in a prospective study of gastrointestinal symptoms with modest improvements in symptoms at 24 weeks compared to baseline using the CF-specific CFAbd-Score[12]. Similar small improvements were reported in the PROMISE study (change of scores at 6 months compared to baseline, PAGI-SYM -0.15, PAC-SYM -0.14, PAC-QOL -0.15)[13]. In the first study by Mainz *et al.*, no sex differences were noted in the reporting of GI symptoms although the PROMISE study demonstrated high scores at baseline within female participants.

Additionally, earlier studies which evaluated the effects of Ivacaftor on those with a gating mutation also demonstrated improvements to the proximal small intestinal pH[14], changes in the gut microbiome and decreased intestinal inflammation[15]. Conversely, in a phase 3 randomised control trial, diarrhoea was reported as one of the most common adverse events in patients on ETI compared to placebo (12.9% vs 7% respectively)[1] and was one of the 15 most commonly reported adverse symptoms identified in a systematic review of the four available CFTR modulators currently in clinical practice[16]. In a recent JLA refresh into research, relieving gastrointestinal symptoms remained a key research priority and additionally, "what are the effects of modulators on systems outside the lungs such as pancreatic function, liver disease, gastrointestinal, bone density etc" was identified as a new top 10 priority in the CFTR modulator era[17]. This indicates that gastrointestinal symptoms continue to be a problem for some pwCF despite widespread commencement on ETI therapy.

The aim of this survey was to further explore gastrointestinal symptoms in pwCF and the impact of CFTR modulators on these and associated quality of life. These results will also contribute to the development of a CF-specific patient reported outcome measure (PROM) that aims to capture the daily burden of gastrointestinal symptoms for

pwCF (visit cftummytracker.org for more information). Having a current knowledge of the landscape of gastrointestinal symptoms is essential in order for this PROM to be relevant to its intended population group (clinicaltials.gov NCT05251467). Preliminary results of this survey were published as a conference abstract from the 2022 North American Cystic Fibrosis Conference (NACFC)[18].

Methods

Patient and public involvement

Patients and the public (as well as health professionals) took part both in the JLA PSP and in the recent refresh exercise, both of which have identified gastrointestinal problems in CF as a priority question for clinical research. People with CF and parents of children with CF were members of the study steering group. A person with CF is a co-author on this paper and helped to design the questionnaire, publicise the project via social media and interpret the qualitative data. They have contributed to writing the manuscript and disseminating the findings.

Survey development

This work was led by a steering group representative of the CF community, consisting of adults and children with CF, parents of pwCF and multidisciplinary HCPs and researchers who are part of a wider research study: a Comprehensive Approach to Relief of Digestive Symptoms in Cystic Fibrosis: CARDS-CF (clinicaltrials.gov NCT05251467). Researchers were healthcare professionals specialising in adult and paediatric respiratory medicine, cystic fibrosis and gastroenterology. In addition, some members of the research team were instrumental in the development of both JLA PSPs in CF, involved in the analysis of the original gastrointestinal symptom survey in CF or completed similar research in the exploration of other priority research questions in which the same methodology was used[19]. Researchers used their own social media accounts to promote the survey but had no direct contact with participants.

The present survey aimed to gather quantitative and supporting qualitative data on gastrointestinal symptoms in the CFTR modulator era. Approximately 90% of pwCF have a mutation eligible for treatment with ETI [CF Trust - Fighting for life-saving drugs], although funding arrangements vary from country to country and the drug is not universally available. The survey for this study was developed by the steering group described above and questions were also drawn from the original 2018 survey[3] (see participant information sheet and 2022 survey[20,21]). This was to allow comparison of results, where appropriate. Members of the CF community co-designed the survey to ensure the most relevant and appropriate questions were used and that the wording was clear. Ethical approval was given by the University of Nottingham Research Ethics Committee (REC) (Ref: FMHS 436-0122, approved 11/02/2022).

An electronic questionnaire was generated using SurveyMonkey.com. Participants were shown an introductory page containing a description of the survey and a weblink to a more detailed participant information sheet including information on how their data would be collected and used, General Data Protection Regulation (GDPR) information and a link to the University of Nottingham privacy policy[21]. Participants were asked to read and give consent prior to taking part. Those under the age of 16 years were advised to get permission from their parents or guardians. Questions were divided into those for HCPs and pwCF (which were further sub-divided by modulator status). The survey consisted of a series of yes/no questions, multiple-choice questions, Likert scales and free text responses and used skip logic to allow participants to navigate to the most appropriate question based on their responses.

Participants were asked questions which were developed around the following themes:

- Presence of gastrointestinal symptoms for pwCF and their effect on quality of life
- Effect of CFTR modulators on gastrointestinal symptoms and quality of life (where appropriate)
- Dietary or medication changes to manage gastrointestinal symptoms

Data collection

The survey was open for one month between March and April 2022 and was promoted through social media platforms such as Twitter using the Twitter handles @CFAware, @QuestionCF, @CARDSCFresearch and professional accounts, as well as on Instagram and Facebook. In addition, the survey was promoted to health professionals via professional organisations such as the UK CF Medical Association. In order to gain the experiences of as many people as possible, the survey was open to all pwCF, their friends and family and HCPs caring for pwCF. There was no predetermined target sample size. The survey was anonymous although participants were given the option of leaving their contact details in order to receive the results or be involved in any future research opportunities relating to the survey. Participants were made aware that these would be separated from their survey results to maintain anonymity. In addition to questions relating to a person's experience of gastrointestinal symptoms in CF, participants were asked to self-report on basic demographic information such as country they lived in, age, and gender (recorded as "male", "female", "prefer not to say" and "other" with the free text option to self-identify if they wished).

Data analysis

Data were downloaded into Microsoft Excel and participant responses were separated from their contact details prior to analysis and stored as per GDPR guidelines. Analysis was informed by an analytical approach which was previously developed and used by the group through a combination of descriptive statistics, qualitative content analysis and thematic analysis, where appropriate[19,22]. Closed responses were analysed using Microsoft Excel and descriptive statistics were used for interpretation. Data generated

from pwCF and HCPs were reviewed separately and responses from pwCF were separated by modulator status. Where questions for this survey were also included in the 2018 symptom survey, the raw data for each data set were described and compared.

Questions which offered an additional free text response were downloaded into NVivo 12 package (QSR International, Massachusetts) for thematic analysis in order to help support overall understanding of the question. The free text responses for each question were initially reviewed to identify possible themes within the responses. The word frequency function was used to aid with this. Related words (such as bloat, bloated, bloating) were combined whilst other words which were felt to be either artificially increased as they were included within the question (for example diet or medication) or did not relate to the results (verbs such as get, made), were removed.

Through this review of the free text responses, we identified overarching areas of interest in the data (termed themes) and more specific areas of interest within this (termed codes). All the free text responses for the survey were then reviewed and mapped to these codes. Given the variation in the length of free text responses submitted, some responses were relevant to more than one code, therefore these data could be mapped to multiple codes or themes as appropriate. As well as the identification of key themes in the results, alternative or more minority opinions were also considered. The coding and analysis of free text responses were performed independently by two authors and checked by a third researcher in order to ensure consistency and appropriateness of how the data were assigned to each code or theme.

Results

A total of 167 people consented to take part in the survey, with 164 people completing some aspect of the survey, comprising 88 pwCF (54%), 22 (13%) parents or other family members and 54 (33%) HCPs. The median age of pwCF (as self-reported or reported by a family member) was 33 years (range 3 – 62 years), female participants 90/127, (71%), male participants 37/127 (29%). We received responses from 11 countries although the majority of responses received were from the UK (107/126, 85%). There was a greater proportion of responses from UK patients than in the 2018 survey (previously 171/276, 62%). Dietitians accounted for almost half of the responses from HCPs (24/54, 44%). Not all participants answered every question available to them and so the denominator has been included where response numbers and percentages are given. Similarly, the number of free text responses and the amount of detail provided varied greatly between respondents. The respondent demographics are in Table 1.

Table 1. Demographic information.

Demographics	n (%)
Population group (n=164)	
People with CF	88 (54%)
Parents or other relative	22 (13%)
HCP	54 (33%)
- Dietitian - Respiratory physician - Doctor: other - Nurse - Other HCP or researcher - Unknown (missing data)	- 24 (44%) - 13 (24%) - 6 (11%) - 6 (11%) - < 5 - < 5
Gender (n=127)	
Female	90 (71%)
Male	37 (29%)
Country (n = 126)	
United Kingdom USA and Canada Europe (excluding UK) Rest of the world	107 (85%) 11 (9%) 7 (6%) < 5

Of pwCF or their family, 89/110 (81%) pwCF were prescribed a CFTR modulator. ETI was the modulator most commonly reported (73/84, 87%). Most reported starting in 2020, corresponding with the UK-wide funding of ETI through the National Health Service (NHS). Of those pwCF not prescribed a CFTR modulator (n=20), four had their modulator discontinued due to adverse effects, including gastrointestinal adverse effects. Reported gastrointestinal complications were comparable between the 2018 and 2022 surveys (Figure 1).

Symptoms experienced

Of those participants not taking a modulator, 17/19 (89%) reported experiencing gastrointestinal symptoms. For those who were commenced on a CFTR-modulator, 58/84 (69%) reported symptoms prior to commencing therapy and 60/84 (71%) after initiating treatment. The vast majority of HCPs (51/52 98%) said that they cared for patients with gastrointestinal symptoms.

Figure 2a shows the frequency of gastrointestinal symptoms that are experienced at least weekly for pwCF in 2022, separated by modulator status. The most commonly reported symptoms for both groups were: wind/gas, rumbling stomach noises (borborygmi), loose motions (modulator group) and bloating (non-modulator group). For the majority of symptoms, a greater proportion of patients who were not on modulator therapy reported each symptom.

Comparisons between the top 3 reported symptoms by pwCF in the 2018 survey and this survey show that stomach pain and bloating were in the top 3 symptoms for both surveys (Figure 2c). Direct comparison of the question was not possible as some response options which were combined

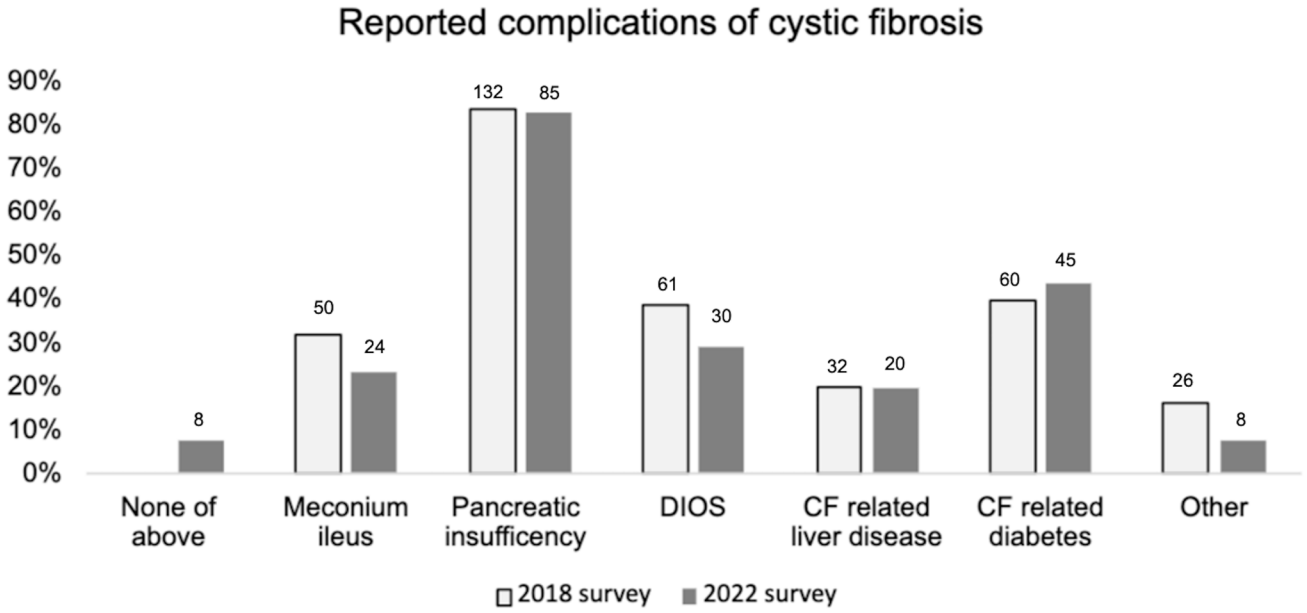

Figure 1. Reported history of CF related complications in the 2018 and 2022 surveys. 2018 survey n=157, 2022 n=103 total responses. "None of above" response option not given as part of 2018 survey. None of above: pwCF did not have one of the 5 listed gastrointestinal complications in the question (meconium ileus, pancreatic insufficiency, DIOS, CF related liver disease or CF related diabetes). Other: free text response for other GI related complications not listed in the question.

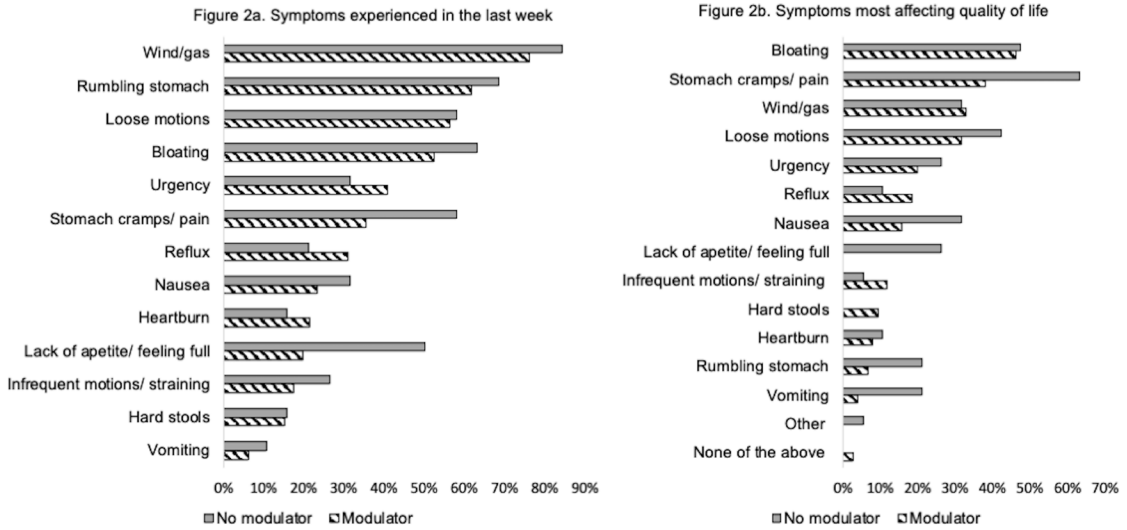

Figure 2c.	2018 survey	2022: Modulator	2022: No modulator
Top 3 reported symptoms	Wind/ gas Bloating Stomach cramps/ pain	Wind/ gas Rumbling noises Loose motions	Wind/ gas Rumbling noises Bloating
Top 3 symptoms affecting quality of life	Stomach cramps/ pain Bloating A combination of symptoms	Bloating Stomach cramps/ pain Wind/ gas	Stomach cramps/ pain Bloating Loose motions

Figure 2. 2a. Symptoms experienced by pwCF at least once a week by modulator status in 2022. **2b**. Symptoms most affecting quality of life by modulator status in 2022 (modulator n= 76) non-modulator n=19) **2c**. Top 3 symptoms reported in 2022 in the modulator group vs no modulator group with comparison to 2018 survey.

in 2018 were separated in this survey. For example, loose/ frequent bowel motions were separated into two response options, whilst other were not included, such as "a combination of symptoms". Symptoms most commonly reported to HCPs by those not on modulators in 2022 were constipation (25/38 66%), bloating (21/38 55%) and stomach pain (18/38 47%).

Those pwCF on CFTR-modulator therapy and HCPs were asked whether they felt gastrointestinal symptoms had improved, stayed the same or worsened since initiating CFTR modulator treatment. PwCF were asked to consider their gastrointestinal symptoms over the previous 4-week period (Figure 3a). For each of the 13 symptom categories, the proportion of pwCF reporting "no change" or "worse" symptoms, following the start of CFTR modulator therapy, was greater than the proportion reporting an improvement.

HCPs shared similar experiences where the greatest proportion of respondents either reported "no change" or "worse" symptoms for most of the symptom categories (Figure 3b). The exceptions to this were reduced appetite, stomach pain and stools that float where the greatest proportion of responses reported an improvement in these symptoms.

In free text responses, HCPs reflected on the variable nature of gastrointestinal symptoms in response to modulators e.g.

HCP quote 1: "symptoms highly variable, for some people things improve and for others they worsen!"

Quality of life

Both groups were asked to what extent they agreed with the statement "gut symptoms affected the QoL for pwCF", with responses on a 5-point Likert scale. Overall, 84/95 (88%) pwCF and 33/35 (94%) HCP said they agreed or strongly agreed with this statement.

Figure 2b and 2c shows the most common symptoms affecting quality of life for pwCF, with comparisons of the top 3 symptoms with the 2018 data. Pain and bloating remained the symptoms felt to most impact quality of life and

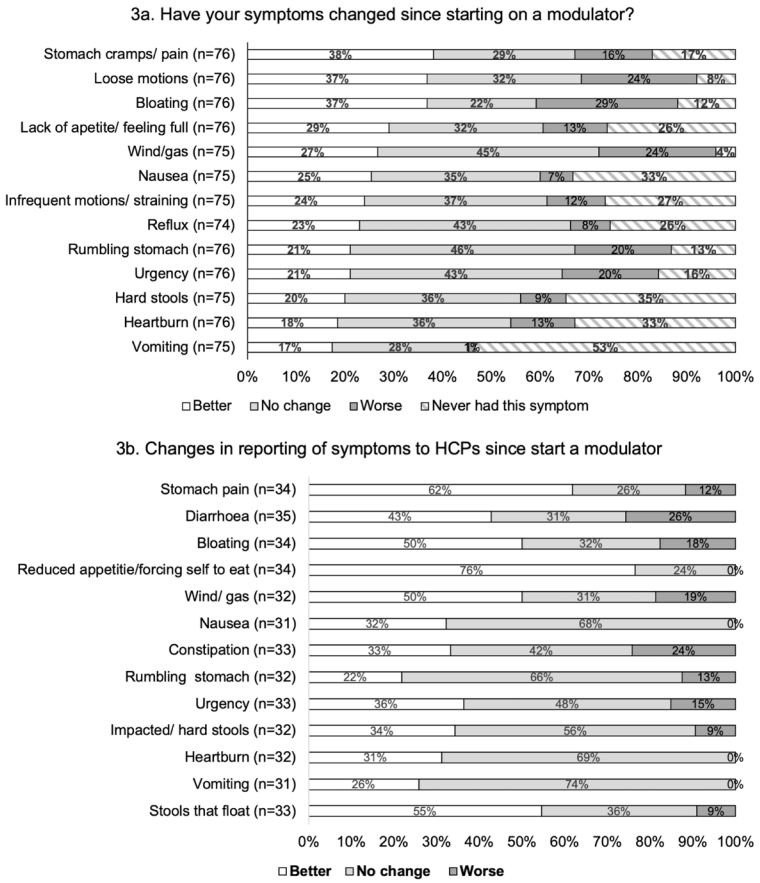

Figure 3. Changes to gastrointestinal symptoms experienced since starting on a CFTR modulator. 3a: PwCF were asked to compare how their symptoms had been in the last 4 weeks, compared to prior to initiating modulator therapy. **3b**: Reporting of gastrointestinal symptoms to HCPs in those people taking a CFTR modulator.

this opinion was also shared amongst HCPs. HCPs identified the top symptoms most affecting quality of life for pwCF to be stomach pain (22/35, 63%), constipation (16/35, 46%) and bloating (15/35, 43%).

Almost two thirds (62/100, 62%) of pwCF felt their gastrointestinal symptoms made them feel embarrassed or affected their self-confidence, although this was experienced to a greater extent in those not receiving CFTR-modulator therapy (modulator: 48/81 (57%) vs no modulator: 14/19 (74%)). These results were very similar to those reported in 2018 (94/145 65%). The theme of embarrassment was further explored through the free text responses.

Bloating was the most commonly reported symptom in the free text responses causing embarrassment for people. Some respondents reported needing different clothes to conceal their bloating. This was also reported in the previous survey before ETI became available[2].

PwCF quote 2: *"When I started Kaftrio I suddenly began to get massively bloated. I looked heavily pregnant and it was a very noticeable change to my body. It affected how I felt about myself both because I was heavily bloated and because it was difficult to dress comfortably or have clothes fit properly."*

PwCF quote 3*: "I'm embarrassed by my gut symptoms with wind, bloating, going to the bathroom multiple times. I get anxiety going to people's homes in case I need to use the facilities and my gut is acting poorly."*

Others talked about the impact of the gastrointestinal symptoms on social situations for example using the toilet in social situations, feeling worried about going out, or the unpredictability of symptoms. In 2018 two thirds of respondents missed school or work because of their gastrointestinal symptoms (97/146). In this survey, this was reduced to 31% (29/94), although this was higher in the non-modulator cohort (9/19 47% vs 20/75 27%). However, 43/94 (46%) of pwCF said they missed social occasions because of their gastrointestinal symptoms (modulator: 34/75 45% vs no modulator: 9/19 47%).

Diet and medication changes

For those pwCF on modulators 44/76 (58%) reported having made changes to their medications which was similar to that reported by HCPs (19/35 54%). Half of pwCF (38/76, 50%) had made changes to their diet to manage gastrointestinal symptoms. This was lower than the proportion of HCPs (28/35, 80%) who reported making changes to the dietary advice they gave for gastrointestinal symptom management.

Dietary changes made by pwCF were focused around two main themes. 1) Reducing the amounts of certain food groups such as carbohydrates, dairy and trialling an increased plant-based diet, and 2) maintaining a healthy diet through the reduction of fats and calorie intake to counteract the increased weight gain experienced on starting a modulator. A healthy diet was also promoted by HCPs following CFTR modulator initiation, who in addition to advising on reducing calories and fats, also promoted the use of "healthy fats" and one HCP also reported promoting exercise to help with weight loss.

Common medication changes reported by pwCF after starting a modulator included the introduction or increasing the dose of proton pump inhibitors, in particular omeprazole for acid reflux (omeprazole word frequency, 7 times), and increased use of laxatives for the management of constipation. The word laxative and its synonyms were used 7 times in the free text responses for this question. Conversely, one person reported being able to stop laxatives since starting modulator therapy.

PERT was also discussed by pwCF and HCPs. The two main themes surrounding PERT use were:

1) Changes made by HCPs to PERT doses: for example, reviewing, altering, reducing or stopping PERT

HCP, quote 4: *"We have managed to reduce or stop Creon in some cases but not all."*

2) Changes made to PERT doses directly by their patients without the advice of HCPs. Reasons given for this included patient's experiences of gastrointestinal symptoms, the perceived need for PERT had changed, or to counteract the weight gain seen following the introduction of modulator therapy.

Discussion

This survey confirms that pwCF frequently experience gastrointestinal symptoms with the most common symptoms being similar to those described in our 2018 survey[3]. These symptoms can affect quality of life for pwCF through disrupting school, work and social events and lead to feelings of embarrassment or self-consciousness. Although for some people gastrointestinal symptoms have improved, most noticeably for symptoms of pain, bloating and loose motions, overall, the proportion of respondents reporting "no change" or "worse" symptoms in each category of this survey, was greater than the proportion reporting an improvement after starting modulators.

Recent results from the PROMISE study, a prospective observational study of pwCF taking ETI demonstrated a small but statistically significant improvement in gastrointestinal symptoms which was felt unlikely to translate into a clinically meaningful benefit for patients[13]. In contrast, in a prospective study of gastrointestinal symptoms, following the introduction of ETI, using a CF-specific questionnaire (CFAbd-Score)[12], Mainz *et al.* demonstrated an improvement in gastrointestinal symptoms. In keeping with this survey, improvements were most evident for abdominal pain (20% improvement in abdominal pain intensity scores and 13% improvement

in abdominal pain experienced scores). Bloating was also reduced by 12%[12].

Some symptoms such as lack of appetite/ feeling full were reported to a lesser extent in those on a modulator compared to those not receiving treatment (20% vs 50%) (Figure 2), suggesting this symptom may be experienced less frequently in those not on a modulator. However, the proportion of participants reporting a positive change in this symptom after starting on therapy was lower than those reporting no change or worsening symptoms. We hypothesis that the improved appetite in the modulator group (Figure 2) may more likely reflect the overall gastrointestinal symptoms experienced being less in this group and not inhibiting their desire to eat.

The results suggest that healthcare professionals may overestimate the effect of modulators on GI symptoms compared to pwCF. Although this in part may be as a result of selection bias in pwCF as described below, it is important for clinicians to be mindful of this and implore the use of CF specific patient reported outcome measures to objectively assess their patient's experiences of GI symptoms.

It was encouraging to see in this survey that the percentage of pwCF missing school or work because of gastrointestinal symptoms had decreased compared to previously, although this was to a greater extent for those on modulators. This may also reflect the improvement in some gastrointestinal symptoms in this group. Unfortunately, the embarrassment experienced as a result of gastrointestinal symptoms showed little change compared to the results of the 2018 survey. Interestingly, embarrassment was increased in the study by Mainz *et al.* at 24 weeks following ETI initiation[12]. They attributed this to a higher expectation of participants following a clinical improvement on therapy[12].

The majority of HCPs reported that following commencing of modulator therapy, they had altered their medication prescribing practices as well as dietary advice, in order to manage gastrointestinal symptoms. In some cases, HCPs were able to adjust a patient's PERT, including reducing or stopping the medication. However, in other cases the patients were instigating changes to PERT prior to health care advice. PERT was previously identified as one of the most burdensome treatments for pwCF[23].

Limitations

This study provides a snapshot of the occurrence of gastrointestinal symptoms in pwCF but inevitably the information is reliant on participant recall. We acknowledge that many pwCF were commenced on modulators in 2020, indicating a long recall time to the pre-treatment period (over a year). This could lead to recall bias. Similarly, it is possible selection bias exists in that firstly those individuals who have gastrointestinal symptoms which are particularly troublesome are more likely to respond to the survey compared to those where symptoms were not an issue. This could be reflected also in the proportion reporting CF complications such as meconium ileus (a risk factor for DIOS) which was higher in our survey (24/103, 23%) than in the UK CF registry (19%)[6]. Nevertheless, the prevalence of pancreatic insufficiency was similar to that of the UK CF registry (2022 survey: 85/103 83%, UK CF registry 85%)[6].

Some participants did not complete every question available to them, accounting for the differing denominators given within the results. This limitation in survey completion may lead to symptoms either being overrepresented, or conversely may mean that any improvements may not be detected as those with resolved symptoms may be less inclined to complete the survey.

Additionally, although comparisons were drawn between the 2018 and 2022 data, we acknowledge that in order to maximise engagement and completion of the survey, the study populations were not standardised. This lack of standardisation may account for the large reduction in the reporting of notable GI complications such as meconium ileus and DIOS in 2022 compared to 2018. However, as the annual incidence of DIOS reported within the UK CF registries declined slightly in 2021 compared to 2018 (5.2% 2018[24] vs 4.8% 2021[6]) this may partially account for the decline in DIOS reporting in this survey. In future, longitudinal studies are needed to assess the prevalence and changes in GI symptoms in CF.

Furthermore, although this survey was open to all pwCF, there was a greater response by females compared to male participants (females: 90/127, 71% vs males: 37/127, 29%). This may reflect the findings of recently published studies in CF that GI symptom scores were found to be higher in female participants[4,13]. However, we do acknowledge that sex differences were not seen in all studies, with studies by Mainz *et al.* finding no difference in GI symptoms based on sex[2,12]. The lower number of male participants prevented sub-analysis of the results by modulator status and gender and so conclusions around GI symptoms based on gender cannot be drawn in this survey.

In the present study, although the number of individuals not on CFTR modulators (19%) was higher than expected, as approximately 90% of the CF population should be eligible for this treatment [CF Trust - Fighting for life-saving drugs] this still represented a small number of the CF population (n=20 participants) and therefore these results may not be generalisable and difficult to compare against those on modulators and the results of the 2018 survey. In addition to eligibility based on genotype, people may also have not had access to modulators due to the lack of funding in their healthcare system or they may have had modulator treatment discontinued, due to adverse effects. Finally, this survey was promoted and disseminated online and so its availability was limited to those who had access to digital technology. This may have limited those who choose not to engage with social media, lack internet access or a digital device and those from

low- and middle-income countries from being able to give their experiences in the survey[25]. Furthermore, although dissemination of the survey online allowed for international participation by the CF community, the majority of responses were from the UK (85%).

Conclusion

This survey highlights that gastrointestinal symptoms still remain prevalent in the CFTR modulator era in pwCF. A better understanding of the underlying pathophysiology of these symptoms is essential in order to improve gastrointestinal symptoms for pwCF. Future clinical studies into gastrointestinal symptoms should focus on understanding and improving both the symptomatology and quality of life for pwCF.

Data availability

Underlying data

Ethical approval was granted by the University of Nottingham Research Ethics Committee. The approved patient information sheet detail that data will be stored within the University of Nottingham and that no participant with be personally identifiable from the results. This is also detailed in the approved data management plan and therefore the raw data has not been made publicly available. A redacted version of the data can be obtained by reasonable request to the study Principal Investigator and corresponding author Professor Alan Smyth (alan.smyth@nottingham.ac.uk). This will be assessed on a case-by-case basis. Applications should state the research question being addressed and include a link to the researcher's published protocol. This will be reviewed by the research team and a final decision to share data the responsibility of the Principal Investigator.

Extended data

figshare: Participant information sheet for online survey "The use of CFTR modulators and gut symptoms in Cystic Fibrosis. https://doi.org/10.6084/m9.figshare.22263952.v1[20]

figshare: 2022 GI symptom survey in cystic fibrosis.pdf. https://doi.org/10.6084/m9.figshare.22263886.v1[21]

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Open Peer Review

Current Peer Review Status: ✔ ? ✔ ? ?

Version 2

Reviewer Report 01 March 2024

https://doi.org/10.3310/nihropenres.14664.r31165

✔

Drucy Borowitz
University at Buffalo, Buffalo, New York, USA

I accept this revised manuscript.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: CF clinical trials; PERT trials; evaluation of GI symptoms; methods to include the lived experience of pwCF

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 01 September 2023

https://doi.org/10.3310/nihropenres.14515.r29560

?

Barbara Ruaro
University Hospital of Cattinara, Trieste, Italy

This is an interesting paper. The manuscript is quite well written. I have few suggestion:

A) 1- Introduction

"*Cystic fibrosis (CF) is an autosomal recessive, life-limiting condition affecting approximately 100,000 people worldwide, caused by mutations to the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein*[1]"

Please improve this paragraph and some references. Please, add some information regarding the different aspects of *Cystic fibrosis.* I suggest:

1. Combined use of rheology and portable low-field NMR in cystic fibrosis patients. *Respir Med*. 2021;189:106623. doi:10.1016/j.rmed.2021.106623

2. Prevalence and Impact of Rheumatologic Pain in Cystic Fibrosis Adult Patients. *Front Med (Lausanne)*. 2022;8:804892. Published 2022 Feb 8. doi:10.3389/fmed.2021.804892

B) Please, add some information regarding the statistical analyses. The Authors need to add some information on statistical tests used to analysed the data and better clarify the value of the results

C) Discussion

"*This survey confirms that pwCF frequently experience gastrointestinal symptoms with the most common symptoms being similar to those described in our 2018 survey*[3]*. These symptoms can affect quality of life for pwCF through disrupting school, work and social events and lead to feelings of embarrassment or self-consciousness. Although for some people gastrointestinal symptoms have improved, most noticeably for symptoms of pain, bloating and loose motions, overall, the proportion of respondents reporting "no change" or "worse" symptoms in each category of this survey, was greater than the proportion reporting an improvement after starting modulators.*"

Improve the summary of the most important study results. Please, add some information regarding the *most important statistically significant study results*

D) Conclusion

"*This survey highlights that gastrointestinal symptoms still remain prevalent in the CFTR modulator era in pwCF. A better understanding of the underlying pathophysiology of these symptoms is essential in order to improve gastrointestinal symptoms for pwCF. Future clinical studies into gastrointestinal symptoms should focus on understanding and improving both the symptomatology and quality of life for pwCF.*"

Underline the novelty of the study and the possible clinical implications.

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pulmonology diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 19 Nov 2023

Alan Smyth

This is an interesting paper. The manuscript is quite well written. I have few suggestion:

Introduction:

Comment.

“Cystic fibrosis (CF) is an autosomal recessive, life-limiting condition affecting approximately 100,000 people worldwide, caused by mutations to the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein1"

Please improve this paragraph and some references. Please, add some information regarding the different aspects of Cystic fibrosis. I suggest:
Combined use of rheology and portable low-field NMR in cystic fibrosis patients. Respir Med. 2021;189:106623. doi:10.1016/j.rmed.2021.106623

Prevalence and Impact of Rheumatologic Pain in Cystic Fibrosis Adult Patients. Front Med (Lausanne). 2022;8:804892. Published 2022 Feb 8. doi:10.3389/fmed.2021.804892

Response.

Thank you for suggesting these references. The first suggested reference describes the use of low-field NMR to measure the physical properties of respiratory tract secretions in CF. As such, it is not relevant to the current paper which reports the perception of gut symptoms by people with CF. The second proposed citation is a paper on rheumatological pain – again this is not relevant to a paper on gut symptoms. We have not added these citations.

Comment.

Statistical analyses:
Please, add some information regarding the statistical analyses. The Authors need to add some information on statistical tests used to analysed the data and better clarify the value of the results.

Response.

The results section includes descriptive statistics only. The methods used are described in the section on “Data analysis”.

Discussion:

Comment.

This survey confirms that pwCF frequently experience gastrointestinal symptoms with the most common symptoms being similar to those described in our 2018 survey3. These symptoms can affect quality of life for pwCF through disrupting school, work and social events and lead to feelings of embarrassment or self-consciousness. Although for some people gastrointestinal symptoms have improved, most noticeably for symptoms of pain, bloating and loose motions, overall, the proportion of respondents reporting “no change” or “worse” symptoms in each category of this survey, was greater than the proportion reporting an improvement after starting modulators."

Improve the summary of the most important study results. Please, add some information regarding the most important statistically significant study results

Response.

As notes above this paper presents descriptive statistics only and statistical tests of significance have not been applied.

Conclusion:

Comment.

"This survey highlights that gastrointestinal symptoms still remain prevalent in the CFTR modulator era in pwCF. A better understanding of the underlying pathophysiology of these symptoms is essential in order to improve gastrointestinal symptoms for pwCF. Future clinical studies into gastrointestinal symptoms should focus on understanding and improving both the symptomatology and quality of life for pwCF."

Underline the novelty of the study and the possible clinical implications.

Response.

Thank you for this suggestion. We believe the conclusion makes an appropriate comparison with the findings of our previously published survey. The implications are primarily for research rather than clinical practice.

Competing Interests: This response is from the corresponding author.

Reviewer Report 10 August 2023

https://doi.org/10.3310/nihropenres.14515.r29758

?

Dana Albon
UVA, Virginia, USA

This is a very well written manuscript. It describes the results of a survey aiming to investigate the presence of gastrointestinal symptoms in teenagers and adults with CF post modulator therapy use. Most people with CF answering the survey were on ETI.

I recommend minor revisions to the manuscript.

Under results, I recommend for the authors to review the numbers again; they do not add and from line to line they differ. Example: for PwCF 89/110 were prescribed a modulator, however the ETI was reported in 73/84. If 89 were prescribed a modulator, the reported ETI use would need to be 73/89 and not 84. There are several discrepancies like this. Please also review the demographics table; same discrepancies are seen in the table; PwCF are listed at 88 and not 89. Similar discrepancies exist throughout the results.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a Pulmonary Critical Care physician who has been taking care of CF patients for more than 10 years.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 19 Nov 2023

Alan Smyth

I recommend minor revisions to the manuscript.

Comment.
Under results, I recommend for the authors to review the numbers again; they do not add and from line to line they differ. Example: for PwCF 89/110 were prescribed a modulator, however the ETI was reported in 73/84. If 89 were prescribed a modulator, the reported ETI use would need to be 73/89 and not 84. There are several discrepancies like this. Please also review the demographics table; same discrepancies are seen in the table; PwCF are listed at 88 and not 89. Similar discrepancies exist throughout the results.

Response.
Thank you for this comment. The data have been reviewed as advised. The discrepancies above were related to the questions not being mandatory and so not all participants answered every available question to them. We have opted to include the denominator as those who answered a particular question, as described in paragraph 1 of the results section, in line with our previous published research. The text in the results section has also been improved to clarify the discrepancies in the number of pwCF, for example 110 people related to the number of lay people (pwCF or a parent/relative) who answered this question, as some parents completed this survey on behalf of their child.

Competing Interests: This response is from the corresponding author.

Reviewer Report 10 August 2023

https://doi.org/10.3310/nihropenres.14515.r29985

Drucy Borowitz
University at Buffalo, Buffalo, New York, USA

This manuscript addresses a timely topic and its strength is that it is grounded in the lived experience of pwCF. My specific comments are as follows:

Abstract: I'd delete focusing on changes made in medications in the abstract and add some of the most relevant findings e.g. the improvement in appetite, and the discrepancy between the perception of 38% of pwCF that stomach pain improved whereas 62% of HCPs thought it was improved. (See my comments below)

Plain language summary: Well-written, although I might conclude that based on this study's results, future research into the effects of CFTR modulators needs to focus on GI and QoL issues.

Introduction: No changes needed

Methods: Well-described

Results:

1. I cannot determine how many respondents were not taking modulators. After the bold section titled "Symptoms Experienced", 19 is reported as the denominator. (Note that there seems to be a word missing at the start of this sentence). One sections states, "*Of those not prescribed a modulator (n=20)...*", though I suspect this means those not taking a modulator since 4 were reported as having discontinued treatment, therefore they must have had modulators prescribed at some point. The explanation for Figure 2c says 38 subjects were not on a modulator. This discrepancy needs to be resolved.

2. Figure 2c should include the n for each column so that the reader doesn't have to go back to Figure 1 (especially since the number of people not on modulators is much lower than the number reporting in 2018). 3) The section on Diet and Medication changes is interesting, especially the reported changes in diet. However, I would delete the paragraph that start, "*For pwCF taking a CFTR modulator and HCPs, the symptoms of constipation...*" This doesn't add anything and it is unclear how many pwCF responded/ how many HCPs responded in free text.
   The number is likely to be too small for this to have any generalizable information. I would also entirely delete the section on HCPs and PERT. The lack of objective measures or correlation with specific patients is confusing. It is more important to report that some pwCF made changes to their PERT doses without the advice of HCPs (your item 2 in this section; the last paragraph). This may be useful to HCPs who may be unaware that pwCF are doing this and can open future conversations.

Discussion:

1. Some of the key findings are not discussed. e.g. Figure 1 shows that DIOS fell from 39% in 2018 to 29% in 2022. Although meconium ileus fell similarly it is unlikely that this neonatal condition changed in that short a period of time. However, the decline in DIOS, even if it is an artifact, deserves some discussion especially since this is a significant GI complication

2. Figure 2 indicates that lack of appetite and stomach cramps appears to be less in people on modulators. Again, the numbers in the groups are not comparable, but why do the authors

speculate this might be?

3. Based on Figure 3, 38% of pwCF thought stomach pain had improved on modulators vs. 62% of HCPs thought stomach pain had improved. The authors should discuss this discrepancy and how it might stimulate future patient-HCP conversations.

4. The limitations paragraph should note that it is difficult to compare those on and off modulators because the size of the groups is not the same and the data may be skewed by the small number of subjects not on modulators.

Figures: Figure 3: I might title 3b "*How pwCF describe their symptoms to HCPs*". Figure 4 is unnecessary. The text does a better job of describing the themes.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: CF clinical trials; PERT trials; evaluation of GI symptoms; methods to include the lived experience of pwCF

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 19 Nov 2023

Alan Smyth

Abstract:
Comment.
I'd delete focusing on changes made in medications in the abstract and add some of the most relevant findings e.g. the improvement in appetite, and the discrepancy between the

perception of 38% of pwCF that stomach pain improved whereas 62% of HCPs thought it was improved. (See my comments below).

Response.
Thank you for this observation. We have made reference to the discrepancies in the changes GI symptoms reported between HCPs and pwCF however in response to other reviewer comments we have opted to keep the information on dietary and medication changes in the abstract.

Plain language summary:
Comment.
Well-written, although I might conclude that based on this study's results, future research into the effects of CFTR modulators needs to focus on GI and QoL issues.

Response.
Thank you for this comment. This has been added to the plain language summary as requested.

Results:
Comment.
I cannot determine how many respondents were not taking modulators. After the bold section titled "Symptoms Experienced", 19 is reported as the denominator. (Note that there seems to be a word missing at the start of this sentence). One sections states, "Of those not prescribed a modulator (n=20)...", though I suspect this means those not taking a modulator since 4 were reported as having discontinued treatment, therefore they must have had modulators prescribed at some point.

Response.
Apologies for the confusion with the demographic information in paragraph two of the results. You are correct in your interpretation that 20 respondents reported not taking a CFTR modulator, although 4 of these reported being prescribed one in the past but stopped due to adverse reactions. As not every respondent answered every question available to them the denominators given in the results section reflects the total number if respondents per question, rather than the total number of people in each group (modulator, non-modulator, HCP). This accounts for the differences of 19 vs 20 people not on a modulator. This is described in paragraph one of the results.

Comment.
The explanation for Figure 2c says 38 subjects were not on a modulator. This discrepancy needs to be resolved. Figure 2c should include the n for each column so that the reader doesn't have to go back to Figure 1 (especially since the number of people not on modulators is much lower than the number reporting in 2018)

Response.
Thank you for these comments. As not every participant answered every question available to them, the denominator has been added in brackets to figure 2a and 2c and in the legend for figure 2b. The years have been added to the figure legends.

Comment.
The section on Diet and Medication changes is interesting, especially the reported changes in diet. However, I would delete the paragraph that start, "For pwCF taking a CFTR modulator and HCPs, the symptoms of constipation..." This doesn't add anything and it is unclear how many pwCF responded/ how many HCPs responded in free text."

Response.
This paragraph has been deleted as suggested.

Comment.
The number is likely to be too small for this to have any generalizable information. I would also entirely delete the section on HCPs and PERT. The lack of objective measures or correlation with specific patients is confusing. It is more important to report that some pwCF made changes to their PERT doses without the advice of HCPs (your item 2 in this section; the last paragraph). This may be useful to HCPs who may be unaware that pwCF are doing this and can open future conversations.

Response.
We have deleted the sentence regarding HCPs and PERT use but have kept the section describing the two overall themes relating to PERT use identified in the free text comments i.e. changes made by HCPs and changes made by patients.

Discussion:
Comment.
Some of the key findings are not discussed. e.g. Figure 1 shows that DIOS fell from 39% in 2018 to 29% in 2022. Although meconium ileus fell similarly it is unlikely that this neonatal condition changed in that short a period of time. However, the decline in DIOS, even if it is an artifact, deserves some discussion especially since this is a significant GI complication.

Response.
We acknowledge that although a small decline in DIOS was reported in the 2021 (most recent registry report) compared to 2018, these results are more likely because of the populations not been standardised between the two surveys. This has been added to the limitation section, paragraph 1.

Comment.
Figure 2 indicates that lack of appetite and stomach cramps appears to be less in people on modulators. Again, the numbers in the groups are not comparable, but why do the authors speculate this might be?

Response.
Thank you for this comment. The mechanism for improved appetite is not yet established but may be due to a reduction of overall GI (and respiratory) symptoms and therefore an improved desire to eat. However, overall we found that the proportion of people reporting an improvement in these 2 symptoms was lower than those reporting no change or worsening of symptoms. This has been addressed in the first paragraph of the discussion.

Comment.
Based on Figure 3, 38% of pwCF thought stomach pain had improved on modulators vs. 62% of HCPs thought stomach pain had improved. The authors should discuss this discrepancy and how it might stimulate future patient-HCP conversations.

Response.
A paragraph has been added to the discussion section (paragraph 3) to reflect this. Although this could be selection bias of pwCF, we would recommend the use of CF specific PROMs to assess more objectively the patient's experiences of GI symptoms.

Comment.
The limitations paragraph should note that it is difficult to compare those on and off modulators because the size of the groups is not the same and the data may be skewed by the small number of subjects not on modulators.

Response.
The size of the groups were expected to differ given that 90% of the CF population should be eligible for this treatment based on their genotype (paragraph 3 limitation section). However, we do acknowledge that the total number of people in the non-modulator group was small and therefore potentially not generalisable. This has been included within this paragraph to reflect this.

Figures:
Comment.
Figure 3: I might title 3b "How pwCF describe their symptoms to HCPs".

Response.
Figure 3b titled has been updated as advised.

Comment.
Figure 4 is unnecessary. The text does a better job of describing the themes".

Response.
We have removed figure 4 as advised.

Competing Interests: These responses are from the corresponding author.

Reviewer Report 10 August 2023

https://doi.org/10.3310/nihropenres.14515.r29764

Mette Frahm Olsen
University of Copenhagen, Copenhagen, Denmark

The manuscript “A grumbling concern: an international survey of gastrointestinal symptoms in cystic fibrosis in the modulator era” describes the findings of a study investigating GI symptoms from the lived experience and its impact of quality of life. The study finds that GI symptoms remain a problem in CF and highlights the need for a better understanding of the pathophysiology of GI symptoms.

Relief of GI symptoms is a highly prioritised topic among those living with CF, their families/friends and CF professionals. Authors should be commended for involving the CF community in this study as members of a study steering group and as a co-author of the paper.

General comments

It seems a bit of a stretch to call this “an international survey” as it was only in English and mainly promoted on UK platforms. The large majority of respondents (85%) were from the UK and the rest mainly from North America. It leaves about 10 respondents from other European countries. “<5% rest of world” is mentioned but other categories sum to 100%. I would suggest toning down that it was international (from title etc). If it was a main aim, the survey should have been planned differently to better represent the international CF community.

No direct comparisons were possible, but data suggest that GI symptoms persist after introduction of CFTRm. However, a main issue with the study is selection bias as people self-select to answer a survey about GI symptoms, i.e. issues are likely to be overrepresented and potential improvement could be overlooked. Selection bias is mentioned in study limitations, but not the risk of not detection improvements, e.g. if those with resolved symptoms are less likely to answer the survey.

Abstract

Changes in dietary intake and medication are reported. It is later mentioned that these are with the intention of managing GI symptoms. Please add this information to the abstract.

Introduction

You argue that “*These results will inform the development of a CF-specific gastrointestinal patient reported outcome measure for people with CF that can be used in clinical trials.*” But as mentioned just above, several CF-specific tools exist. Please clarify how the new tool will be different from the currently available tools? (e.g. Mainz et al. CFAbd score, Quittner et al. GI symptom tracker), and why there is a need for more PROMs?

Results

The results are partly based on qualitative data from free-text fields in survey. Please indicate how much data this is based on, e.g. how many respondents used this option and how much text did they provide?

There are 167 participants in the study, but the denominator is much lower for many variables. Was modulator treatment only known for 110? And only 103 provided responses for GI symptoms? Please clarify and mention in study limitations if this is the case.

Fig 2. Symptoms by modulator status. Based on 2022 data? Or also 2018 data? Not clear. If only 2022, no modulator data is based on 20 participants? Number of participants should be included in the figure or figure legend.

Fig 3. HCP seem to overestimate the effects of modulators on GI symptoms. But this could be due to selection bias among CF patients > HCP.

Discussion

It is not the same respondents or questions in the 2018 vs 2022 surveys, which makes a comparison difficult. Authors do mention this limitation, but I think it would be reasonable to add that longitudinal studies are needed to assess prevalence and changes in GI symptoms in CF.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Not applicable

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cystic fibrosis; public health; epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 19 Nov 2023

Alan Smyth

General comments:
Comment.
It seems a bit of a stretch to call this “an international survey” as it was only in English and mainly promoted on UK platforms. The large majority of respondents (85%) were from the UK and the rest mainly from North America. It leaves about 10 respondents from other European countries. “<5% rest of world” is mentioned but other categories sum to 100%. I would suggest toning down that it was international (from title etc). If it was a main aim, the survey should have been planned differently to better represent the international CF community” –

Response.
Thank you for this comment, we have removed international as you suggested given the large representation from the UK.

Comment.
No direct comparisons were possible, but data suggest that GI symptoms persist after introduction of CFTRm. However, a main issue with the study is selection bias as people self-select to answer a survey about GI symptoms, i.e. issues are likely to be overrepresented and potential improvement could be overlooked. Selection bias is mentioned in study limitations, but not the risk of not detection improvements, e.g. if those with resolved symptoms are less likely to answer the survey”.

Response.
This is a valid comment and this has now been reflected in paragraph 1 of the limitations section in the discussion.

Abstract:
Comment.
Changes in dietary intake and medication are reported. It is later mentioned that these are with the intention of managing GI symptoms. Please add this information to the abstract” –

Response.
This has been added as requested

Introduction:
Comment.
You argue that “These results will inform the development of a CF-specific gastrointestinal patient reported outcome measure for people with CF that can be used in clinical trials.” But as mentioned just above, several CF-specific tools exist. Please clarify how the new tool will be different from the currently available tools? (e.g. Mainz et al. CFAbd score, Quittner et al. GI symptom tracker) and why there is a need for more PROMs?

Response.
Thank you for this comment. The CF-specific gastrointestinal PROM, which we are developing (CFTummyTracker), is designed for daily use, with an emphasis on the burden caused by GI symptoms. It would compliment the findings of the GI symptom tracker and CFAbd Score which have a longer recall period of one and two weeks respectively.

Results:
Comment.
The results are partly based on qualitative data from free-text fields in survey. Please indicate how much data this is based on, e.g. how many respondents used this option and how much text did they provide?

Response.
There were multiple free text comments available within the survey asking people to expand on their answers to the quantitative data if they would like to, which were not mandatory. Each free text comment gave a varying number of responses as well as length of the free text comments. For example, questions which a respondent selected “other, please specify” were <5 responses, whereas free text asking the year in which a modulator was started had 84 free text responses. Therefore, we have chosen to include the following sentence explaining this rather than provide individual number of responses per question. “Similarly, the number of free text responses and the amount of detail provided varied greatly between respondents.” This has been added to paragraph 1 of the results section.

Comment.
There are 167 participants in the study, but the denominator is much lower for many variables. Was modulator treatment only known for 110? And only 103 provided responses for GI symptoms? Please clarify and mention in study limitations if this is the case.

Response.
Thank you for this comment. All questions were optional for a participant to complete and so not every participant completed every question available to them and therefore the denominator for each question is included in the results. This has been clarified in the first paragraph of the results section and has been added as a limitation as suggested.

Comment.
Fig 2. Symptoms by modulator status. Based on 2022 data? Or also 2018 data? Not clear. If only 2022, no modulator data is based on 20 participants? Number of participants should be included in the figure or figure legend”

Response.
Thank you for this comment. The denominators have been added to figure 2a and 2c and the legend for figure 2b for clarification.

Comment.
Fig 3. HCP seem to overestimate the effects of modulators on GI symptoms. But this could be due to selection bias among CF patients > HCP.”

Response.
A paragraph has been added to the discussion section (paragraph 3) to reflect this.

Discussion:
Comment.

It is not the same respondents or questions in the 2018 vs 2022 surveys, which makes a comparison difficult. Authors do mention this limitation, but I think it would be reasonable to add that longitudinal studies are needed to assess prevalence and changes in GI symptoms in CF.

Response.
This has now been addressed in paragraph two of the discussion.

Competing Interests: This response is from the corresponding author.

Reviewer Report 12 July 2023

https://doi.org/10.3310/nihropenres.14515.r29317

Dhiren Patel
Saint Louis University, St. Louis, Missouri, USA

I congratulate authors to conduct this survey. This is well needed guidance from patients and CF care providers perspective to CF researcher and shows that ETI may have fixed some issues and unfortunately Gastrointestinal symptom is not one of them.

Few comments for authors:

Although it is named as international survey, the majority of responders were from UK. This could have been an issue with the distribution. I certainly have not seen this survey making its way to me in USA and I am part of the DIGEST group in USA. Having said that, this has been done in USA and authors cite that reference in the manuscript. I don't think its a big issue but I would suggest to specify this as a limitation.

Reviewer Comments: A grumbling concern

Abstract:

1. Consider replacing “rumbling stomach noises” with borborygmi

2. “*loose motions (modulator) and bloating (no modulator)*" – does this mean loose motion is the most commonly reported in patients on modulator etc?

Page 3:

1. Correct spelling of “licencing”

2. “*prior to the licensing of the newest and most widely used modulator ETI*” – no comma needed

3. Resources in [ ] are great, but seem out of place as just a link here. Perhaps consider keeping them as a reference and then putting together a list of the hyperlinks at the end.

4. 5th paragraph, first sentence, consider condensing this sentence
   - 5th paragraph, last sentence, add a source

5. 6th paragraph: consider changing less well to not as well

6. 7th paragraph: Spell our JLA the first time you use it

7. Keep references consistent

Page 4:

1. 1st paragraph: PSP?

2. 2nd paragraph: consider changing patient community to CF community
   - At the end of this paragraph, the reference style is not consistent with other references

Page 5:

1. First paragraph – your point regarding artificially increasing words is a good point

2. Table 1: what does “Other” vs “Unknown” entail?

Page 6:

1. Figure 1: clarify what is in other vs none of the above

Page 7:

1. Figure 3 – interesting discrepancy between HCP vs PwCF reports of changes in symptoms

Page 8:

1. Paragraph 6 – last line – what sort of changes to advice did they give?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
No source data required

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pediatric Gastroenterology, Hepatology and Nutrition, Cystic Fibrosis, Gastrointestinal Motility

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 19 Nov 2023

Alan Smyth

General comments:
Comment.
Although it is named as international survey, the majority of responders were from UK. This could have been an issue with the distribution. I certainly have not seen this survey making its way to me in USA and I am part of the DIGEST group in USA. Having said that, this has been done in USA and authors cite that reference in the manuscript. I don't think its a big issue but I would suggest to specify this as a limitation" –

Response.
Thank you, this was noted in the results section that the majority of respondents were from the UK. This has been added as a limitation as advised. The word international has also been removed from the text.

Abstract:
Comment.
Consider replacing "rumbling stomach noises" with borborygmi"

Response.
This has been included in brackets for clarification in the abstract and main body of the text.

Comment.
"Loose motions (modulator) and bloating (no modulator)" – does this mean loose motion is the most commonly reported in patients on modulator etc?"

Response.
Wind/ gas and borborygmi were the most commonly reported symptoms in both groups, loose motions were also commonly reported in those on a modulator and bloating in those not receiving modulator therapy. The abstract has been updated to clarify this.

Page 3:
Comment.
Correct spelling of "licencing"

Response.
This has been updated to licensing

Comment.

“prior to the licensing of the newest and most widely used modulator ETI” – no comma needed.

Response.
Thank you, this has been updated.

Comment.
Resources in [ ] are great, but seem out of place as just a link here. Perhaps consider keeping them as a reference and then putting together a list of the hyperlinks at the end”

Response.
Thank you for this comment. The journal referencing style requires weblinks and URLs to be included as hyperlinks in the body of the text rather than at the end of the article as a reference and so these have not been amended in the manuscript.

Comment.
“5th paragraph, first sentence, consider condensing this sentence”

Response.
This has been addressed and split into two sentences.

Comment.
“5th paragraph, last sentence, add a source”

Response.
Reference added by Costa et al detailing the eligibility and licencing of the different modulators in the EU and US.

Comment.
“6th paragraph: consider changing less well to not as well”

Response.
Thank you, this has been updated.

Comment.
7th paragraph: Spell out JLA the first time you use it”

Response.
Thank you. This is written out in full when it is first used in paragraph 2 of the introduction.

Comment.
Keep references consistent

Response.
The journal referencing style requires weblinks and URLs to be included as hyperlinks in the body of the text rather than at the end of the article as a reference and so these have not been amended in the manuscript.

Page 4:
Comment.
1st paragraph: PSP?

Response.
This stands for priority settling partnership. This is written out in full the first time it is used in paragraph 2 of the introduction.

Comment.
2nd paragraph: consider changing patient community to CF community

Response.
This has now been updated from “patient” to “CF” community.

Comment.
At the end of this paragraph, the reference style is not consistent with other references.

Response.
This is in line with the journal requirements for referencing webpages and URLs.

Page 5:
Comment.
First paragraph – your point regarding artificially increasing words is a good point.

Response.
Thank you for this feedback.

Comment.
Table 1: what does “Other” vs “Unknown” entail?”

Response.
Other denotes other healthcare professionals from specific disciplines or researchers. Due to the number of responses being less than 5 we were unable to detail these any further to maintain anonymity. “Unknown” refers to those HCPs who did not record what role or discipline they belonged to.

Page 6:
Comment.
Figure 1: clarify what is in other vs none of the above”

Response.
This has been clarified in the legend of figure 1.

None of above: pwCF did not have one of the 5 listed gastrointestinal complications in the question (meconium ileus, pancreatic insufficiency, DIOS, CF related liver disease or CF related diabetes).

Other: free text response for other GI related complications not listed in the question.

Page 7:
Comment.
Figure 3 – interesting discrepancy between HCP vs PwCF reports of changes in symptoms”

Response.
Thank you for your insight here, this observation has now also been included in the abstract and discussion sections.

Page 8:
Comment.
Paragraph 6 – last line – what sort of changes to advice did they give

Response.
This included promotion of a healthy diet, reducing calories and fats, and promoting exercise. These are detailed in the following paragraph after this sentence.

Competing Interests: These comments are from the corresponding author.