An expert consensus definition of failure of a treatment to provide adequate relief (F-PAR) for chronic constipation – an international Delphi survey


SUMMARY

Background
As treatments for constipation become increasingly available, it is important to know when to progress along the treatment algorithm if the patient is not better.

Aim
To establish the definition of failure of a treatment to provide adequate relief (F-PAR) to support this management and referral process in patients with chronic constipation.

Methods
We conducted an international Delphi Survey among gastroenterologists and general practitioners with a special interest in chronic constipation. An initial questionnaire based on recognised rating scales was developed following a focus group. Data were collected from two subsequent rounds of questionnaires completed by all authors. Likert scales were used to establish a consensus on a shorter list of more severe symptoms.

Results
The initial focus group yielded a first round questionnaire with 84 statements. There was good consensus on symptom severity and a clear severity response curve, allowing 67 of the symptom-severity pairings to be eliminated. Subsequently, a clear consensus was established on further reduction to eight symptom statements in the final definition, condensed by the steering committee into five diagnostic statements (after replicate statements had been removed).

Conclusions
We present an international consensus on chronic constipation, of five symptoms and their severities, any of which would be sufficient to provide clinical evidence of treatment failure. We also provide data representing an expert calibration of commonly used rating scales, thus allowing results of clinical trials expressed in terms of those scales to be converted into estimates of rates of provision of adequate relief.

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INTRODUCTION

Chronic constipation (CC) is a common condition which is very prevalent in many societies.¹,² A particular challenge of chronic constipation is that the various symptoms can mean radically different things to different people. Furthermore, the range of symptoms influences the choice of treatment and the perception of benefit.³ Most patients with CC treat their condition by modifying their diet and lifestyle or with OTC remedies.⁴ Patients consult healthcare professionals when these measures fail. Subsequent medical intervention usually involves the rational use of laxatives⁵, ⁶ but surveys show that treatment satisfaction among patients is low.⁷–⁹

The emergence of new pharmacological treatment options,¹⁰–¹⁴ some of which are predominantly initiated in secondary care settings, has led to the need for guidance on when newer expensive or invasive treatments should be offered.

Some of these newer treatments are medications which could conceivably be initiated in primary care if it could be confirmed in that setting that standard treatments, such as laxatives, had failed to provide adequate relief. Other newer treatments are nonpharmacological in nature, such as sacral neuromodulation and pelvic floor surgery. These are only available in secondary care and a reliable definition of failure of treatment to provide adequate relief is critical for defining progression through the algorithm of care.¹⁵ Therefore, there is a need for an expert definition of F-PAR in CC, ideally based on patient reported outcome measures (PROMs), similar to those reported recently for opiate related constipation.¹⁶,¹⁷ And meeting this need is important because it is only when first line treatments have failed to provide adequate relief that second line and secondary care treatment options can be justified.

There are several methods of obtaining expert consensus opinion (Grade IV evidence) in the absence of definitive results from clinical trials, however, most of these depend on subjective review and group discussion methods, which are open to influence and bias. An alternative approach is to use Delphi Surveys.

Delphi Surveys are carried out by sending questionnaires to experts who complete them in private free from any external influence. The results of Delphi surveys are subsequently analysed using descriptive statistics¹⁸–²⁰ in keeping with rigorous scientific methodology. Such a scientific method is likely to be able to establish the true balance of expert opinion and for this reason has been used extensively to support guideline development in medicine. For example, the German Gastroenterology Guideline on irritable bowel syndrome²¹ and the 2012 Consensus statement on the management of Barrett’s dysplasia of the oesophagus were also developed using Delphi methodology.²² The same approach was also used to deal with areas of uncertainty in developing the Rome IV criteria.²³

The aim of this Delphi Survey was to reach an expert consensus on the clinical features required to define F-PAR in CC, which could also be used as the basis for a decision support tool for use by family doctors and other healthcare professionals who see the majority of patients with chronic constipation.

METHODS

Consensus of experts and the Delphi method

The Delphi Survey technique has been used widely in medical and nursing research as a method to obtain a consensus among a group of experts.¹⁹ The technique involves a panel of about twenty experts taking part in an iterative process in which a series of questionnaires is completed by each of them independently in private. The results of each round are presented back to them only in a summary and in an anonymised form.

The results of one round are used to determine which remaining or modified questions are asked in the next round with each consecutive round of questions worded to facilitate an increasing degree of consensus until 75% or 80% of participants agree on each proposition remaining in the process.¹⁹ Because the questionnaires are completed in private and because the results are only fed back in a summary anonymised form, the process is not open to influence by overt peer pressure from the other participants.¹⁹ The risk of bias can also be reduced if an independent facilitator, unconnected with the participants, is appointed to run the methodological side of the project including drafting the questionnaires and analysing the results.¹⁹

A consensus can only be said to be achieved when a pre-determined proportion of participants are in agreement. This proportion varies between studies and also depends on the way the questionnaires are constructed. Thus, median values may be used as cut-off points in continuous or ordinal data, but, where Likert scales are used, it is customary to require 75% or 80% of participants to rate a proposition as one they agree with or agree strongly with in order for a consensus to exist on that point.¹⁹
In the case of this study, the final consensus was based on an 80% level of agreement.

Participants
The participants in this Delphi survey were European experts in CC. The potential participants were identified based on their publishing record, their established clinical expertise in CC, and their seniority in their place of work (academic institution, secondary or tertiary care hospital). Clinicians for consideration were proposed by the various participants in the study, also including the study sponsor (Shire International GmbH).

Once participants accepted the invitation to take part they were referred to a Clinical Research Organisation (CRO) which provided the independent study logistics and supported the activities of the Independent Facilitator. The role of the sponsor was limited to: proposing participants, providing funding for the logistics and for honoraria to be paid to the steering committee members and the study participants (all at fair market rates). No payments were made in relation to the writing of this manuscript. The sponsor reviewed the study protocol developed by the Independent Facilitator after it was signed by Steering Group members (but proposed no changes).

The steering group (n = 5) had three functions: (i) to provide the Facilitator with a source of extensive expert opinion from which to generate the initial Delphi questionnaire (ii) to advise the Facilitator about technical matters of fact in relation to the study results at the end of each round and any implications these findings have for the design of the questionnaire for the next round and (iii) to vote in each round of the study by completing the same Delphi questionnaires as those completed by the panellists (n = 15).

The panellists (n = 15) had one main function: (i) to complete and return each round of Delphi questionnaires as they were e-mailed to them.

A list of the names of the participants in the panel and steering group is given in the appendix and all are listed as authors.

Study duration
The time required to draft the study protocol, recruit the steering group and panel members, run the study and analyse the data was 4 months.

Initial focus group
The initial round of any Delphi Study is designed to gather as many examples of expert opinion on the study subject as possible. In this study the initial round was conducted by running a focus group involving the Steering Group members (Modified Delphi method as described by Keeney).19 The Steering Group members were asked to provide as many examples of CC symptoms, CC rating scales and CC clinical checklists as possible to use as raw material for making the questionnaires to be used in the voting stage of the Delphi Study.

A full list of the questions included in each round of the Delphi Survey is included in data Table 1.

A decision was made to build the consensus in two parts owing to the wide range of possible clinical options for defining ‘failure of a treatment to provide adequate relief for chronic constipation’.

The first part of the consensus building addressed the degree of severity of CC symptoms required for them to count as failure to provide adequate relief. This identified symptom-severity pairs which a majority of the participants accepted as providing evidence of F-PAR of CC.

The second part of the consensus building addressed which of the symptom-severity pairs accepted as evidence of F-PAR of CC were most appropriate for inclusion in the final definition of the Expert Consensus.

STUDY FLOW

Phase one: output of focus group
Based on the material gathered during the focus group the Facilitator prepared a questionnaire for the first round of the Delphi Survey. The questionnaire had 84 propositions and was reviewed and approved by the Steering Group prior to use. The 84 propositions were framed either as reported patient statements or as diagnostic descriptions. The propositions were to be scored using a five point Likert rating scale ranging from Strongly Disagree to Strongly Agree. To avoid any bias due to questions derived from the same rating scale being asked sequentially (and therefore answered on the basis of pre-conceived views about the meaning of that scale), the order in which the questions were presented was randomised. The questionnaires were sent to the Steering Group and Extended Panel members to be completed and returned electronically.

Simple descriptive statistics were calculated for each question. For tabulation, the results were grouped by questions derived from the same rating scale or checklist and then graphs were plotted to compare severity of symptom to level of acceptance as F-PAR. Where a median value of 4 or more for the Likert score was recorded, the symptom-severity pair was accepted as providing evidence of F-PAR. Missing data were coded as ‘neither agree nor disagree’.
Phase two: generating a narrower questionnaire
The Facilitator presented the analysis of the first round questionnaires to the Steering Group. Based on their advice a second round questionnaire was developed and approved in the same way as the first round questionnaire. This questionnaire focussed on determining which of the most highly rated F-PAR symptom-severity pairs from round one had at least 80% of participants scoring it agree or agree strongly (4 or 5 on the Likert scale). The round two questionnaire comprised 17 propositions and these were also presented in random order. It was distributed, completed and analysed in the same way as the first round questionnaire.

Phase three: drafting and approval of the consensus statement
The Facilitator presented the results of the second round questionnaire to the Steering Group who confirmed the results and edited the questionnaire wording into a format suitable for use as a consensus statement and for use as a check list or clinical decision support tool (F-PAR Tool).

RESULTS
The results comprise three sets of information, presented in sequence below.

<table>
<thead>
<tr>
<th>Question</th>
<th>Median</th>
<th>% agree/agree strongly</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) At least 80% consensus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-PAR = patient wishes to stop Rx because of symptom(s)</td>
<td>4</td>
<td>93%</td>
</tr>
<tr>
<td>F-PAR = strains excessively on most occasions</td>
<td>4</td>
<td>93%</td>
</tr>
<tr>
<td>F-PAR = more straining than previously (worsening)</td>
<td>5</td>
<td>87%</td>
</tr>
<tr>
<td>F-PAR = abdominal symptoms of CC not improved on current Rx</td>
<td>4</td>
<td>87%</td>
</tr>
<tr>
<td>F-PAR = no change in BSS on current Rx and BSS is 1 or 2</td>
<td>4</td>
<td>87%</td>
</tr>
<tr>
<td>F-PAR = patient wishes to stop Rx because of side effect(s)</td>
<td>5</td>
<td>80%</td>
</tr>
<tr>
<td>F-PAR = inadequate N bowel movements (&lt; 3/7 per week)</td>
<td>4</td>
<td>80%</td>
</tr>
<tr>
<td>F-PAR = patient having to strain on most occasions</td>
<td>4</td>
<td>80%</td>
</tr>
<tr>
<td>(b) Less than 80% consensus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-PAR = more abdominal symptoms than previously (worsening)</td>
<td>4</td>
<td>73%</td>
</tr>
<tr>
<td>F-PAR = toileting at least 15 min and longer or same as before</td>
<td>4</td>
<td>73%</td>
</tr>
<tr>
<td>F-PAR = worsening in BSS on current Rx and BSS is 1 or 2</td>
<td>4</td>
<td>73%</td>
</tr>
<tr>
<td>F-PAR = worsening of CC symptoms (P) since Rx started</td>
<td>4</td>
<td>73%</td>
</tr>
<tr>
<td>F-PAR = a lot of straining + impact on ADL</td>
<td>4</td>
<td>67%</td>
</tr>
<tr>
<td>F-PAR = CC symptoms made worse by current Rx</td>
<td>4</td>
<td>67%</td>
</tr>
<tr>
<td>F-PAR = CC symptoms made worse by current Rx</td>
<td>4</td>
<td>67%</td>
</tr>
<tr>
<td>F-PAR = inadequate N bowel movement days (P) + frequent straining</td>
<td>4</td>
<td>67%</td>
</tr>
<tr>
<td>F-PAR = inadequate N bowel movement days (P) + frequent straining</td>
<td>4</td>
<td>67%</td>
</tr>
<tr>
<td>F-PAR = inadequate N bowel movement days (P) + stool hard</td>
<td>4</td>
<td>67%</td>
</tr>
<tr>
<td>F-PAR = inadequate N bowel movement days (P) + stool hard</td>
<td>4</td>
<td>67%</td>
</tr>
<tr>
<td>F-PAR = toileting at least 15 min</td>
<td>3</td>
<td>40%</td>
</tr>
</tbody>
</table>

Phase one: output of focus group
The output of the initial focus group was the raw material from which the Facilitator designed the round one questionnaire. The questionnaire was therefore based on an extensive candidate list of CC symptom-severity pairs including items derived from the PAC-SYM rating scale and the Bristol Stool Scale (BSS). This part of the process resulted in an initial questionnaire made up of 84 propositions.

Phase two: generating a narrower questionnaire from phase one
The results from the initial questionnaire of 84 propositions (presented to the panellists in a randomised order) are presented in Table S1 and Figure S1, grouped thematically.

It should be noted that symptoms which are not specific to CC were rated less favourably as evidence of F-PAR than symptoms which form part of the ROME III criteria for CC. A clear severity/response relationship is apparent in Figure S1 with the more severe symptoms being accepted more strongly as being evidence of F-PAR.

The output of the steering committee review of the Round One results determined the items that went into the Round Two questionnaire. In this way, 67 of the initial 84 questions (symptom – severity pairs) posed in
Round 1 were eliminated rapidly from further consideration as candidates for inclusion in a consensus definition of F-PAR. As a result, the questionnaire for the next round only comprised 17 propositions.

Phase three: drafting and approval of the consensus statement
The results of the round two questionnaire made up of 17 propositions are given in Table 1. The cut-off for accepting a consensus in support of a statement was 80% of the panel rating it ‘agree’ (scored as 4) or ‘agree strongly’ (scored as 5). A total of eight statements met this requirement for a consensus, but it should be noted that there was some overlap in the content of these statements. The steering committee therefore condensed the overlapping text into a final consensus definition of F-PAR made up of the following five statements (consensus checklist or F-PAR Tool):

- (i) An inadequate number of bowel movements is reported by the patient most of the time AND complete bowel movements occur on less than 3 days per week.
- (ii) The patient have to strain on most occasions (or straining is getting worse).
- (iii) There is no improvement in the stool consistency on current therapy AND the Bristol Stool Scale score is less than 3 (hard and lumpy or very hard and small).
- (iv) The patient reports insufficient improvement of another sign or symptom of chronic constipation on the current treatment.
- (v) Poor tolerability of the current treatment makes the relief provided unacceptable to the patient.

It should be noted that the term ‘no improvement’ also included ‘worsening’.

The consensus statement was also presented in the form of a questionnaire to be used as a Patient Reported Outcome Measure (PROM), which we have termed the ‘F-PAR Tool’ (Figure 1). This simple one page questionnaire has been designed to be used as a self-reported patient questionnaire and a treatment decision support tool.

DISCUSSION
This Delphi Survey reached an expert consensus on the five key clinical features required to define the failure of any given treatment to provide adequate relief for a given patient with chronic constipation.

The five-item F-PAR tool, based on the five components of the consensus statement, is proposed for use as a clinical decision-making tool by gastroenterologists, family doctors and other healthcare professionals who treat patients with chronic constipation. Use of the proposed F-PAR tool may make it possible to standardise the process of confirming the failure of a treatment to provide adequate relief of CC, and may improve the quality of treatment decision-making.

Although diagnostic criteria have existed for some time for functional gastrointestinal disorders,26 establishing the correct diagnosis and identifying aetio-pathogenesis of CC are key first steps required to optimise the clinical outcome for the patient. As new research has provided a better understanding of the range of primary and secondary causes of CC, so it has also identified new targets for physical and pharmacological treatment of the disease.27–30 With new behavioural, pharmacological and surgical treatments becoming available it is essential to recognise when a treatment is failing to work adequately and thus should be switched. As a consequence, it has become desirable to have an authoritative method for deciding when a change in treatment is justified. We think that the F-PAR consensus that was achieved in our study supplies this need.

It may be objected that the use of a survey methods to develop a consensus means that the consensus lacks authority, however, the make-up of our study group suggests otherwise. Furthermore, the consensus was achieved after only two rounds of questionnaires, indicating the strength of support for the definition of F-PAR in CC among experts from across Europe and among clinicians working in different clinical settings. It also indicates the strength of support for, and the recognition awarded to the need for, a definition of, F-PAR. In summary, this working definition of F-PAR provides an authoritative clinical method for deciding when a change in treatment is justified.

The F-PAR tool has several strengths: first, the way F-PAR is defined allows a key symptom for the patient to be expressed and followed; second, the tool is easy to use, requiring only one positive answer out of a total of five simply posed questions to be recorded as evidence of F-PAR. Despite this simplicity, the F-PAR tool allows identification of individual symptoms beyond the typical (infrequency, straining and stool consistency) as well as potential intolerance of treatments used to date. As such, failure to respond can be captured in the widest sense, for all patients.

This Delphi Survey also provides some useful insights into how Delphi Surveys can be made more efficient
Delphi Surveys require iterative voting on sequential versions of statements or questionnaires meaning that they often take a long time to complete. To meet the challenge of how to obtain a consensus rapidly using a Delphi Survey, we undertook two adaptations to the classical methodology. The first adaptation was to build the consensus in two parts. In the initial focus group stage, the Delphi process sought the widest range of possible clinical options for defining failure of a treatment to provide adequate relief not only in terms of the choice of symptoms but also in terms of their severity. From the wide range of possible symptoms, and the range of possible severities, it is clear that the number of possible combinations of symptoms and severities which could be tested as possible definitions of F-PAR would be very large. Obtaining a consensus by iterative voting on these would have required a large number of rounds of voting. To reduce the number of possible combinations in testing at any one time, we sought consensus on sign and symptom severity before seeking a consensus on sign and symptom choice. As was reported above, the study was completed in only 4 months and this suggests that the sequential approach to establishing a consensus allowed the result to emerge rapidly.

The order of testing also provided an interesting benefit. The scientific interest of the first round result is considerable as they represent an expert derived

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A Do you think the number of bowel movements you are having is OK?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>1B On how many days did you have a complete bowel movement last week?</td>
<td>[___]</td>
</tr>
<tr>
<td>2A Are you having to strain on most occasions?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>2B Is your straining getting worse?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>3A Has there been any improvement in the hardness of your stools?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>3B Please circle the number of the picture that matches most of your stools</td>
<td>7, 6, 5, 4, 3, 2, 1</td>
</tr>
<tr>
<td>4A Do you want to stop treatment because of a symptom not given above?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>4B If so, what is that symptom?</td>
<td></td>
</tr>
<tr>
<td>5A How do you rate the tolerability of your current treatment?</td>
<td>Good/Poor</td>
</tr>
<tr>
<td>5B If poor, is the benefit your current treatment gives you worthwhile?</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

Figure 1 | F-PAR questionnaire.
calibration of adequate relief of CC in terms of symptom severity measured by criteria which were drawn from widely used rating scales such as the PAC-SYM and Bristol Stool Scales. These calibration results could be used in health economic studies to convert trial results into outcomes (numbers with or without adequate relief).

The second adaptation was to present the propositions in the two Delphi questionnaires in a randomised order such that propositions derived from the same rating scale were not adjacent to each other when the questionnaire was being completed. This meant that the experts were not doing the equivalent of completing the rating scale as they answered the questionnaire, but were obliged to address each proposition in isolation. As a result, answer to each question was the result of careful consideration rather than a reflection of preconceived ideas about good and bad outcomes on familiar rating scales.

Finally, an important observation is that the five features of chronic constipation which remained after testing in the second round closely resembled the key symptom list, which is used to establish a diagnosis of chronic functional constipation using the Rome III criteria in force when the study was conducted, and also the most recent version of the Rome criteria in force when the study was accepted for publication, which are based on an evidence based knowledge but consensus method (‘Delphi approach’), exactly the same method we used in our F-PAR in CC study. This is an important outcome as it ensures that the definition of F-PAR produced by our Delphi Survey is specific to chronic constipation, being closely linked to the key, validated diagnostic criteria for the condition.

We think that the F-PAR in CC tool has great potential of usefulness in clinical practice, by allowing accurate identification of patients who require a change in treatment. Indeed, the way the consensus statement is framed makes it easy to use it as a patient completed clinical check list or as a clinical decision support tool. It is suitable for use in secondary but also in primary care, to decide if a patient should be referred to secondary care for an expert opinion on the future direction of treatment or for more sophisticated testing that might be required to establish the most appropriate choice of second line treatment.

A validation study of the new tool in a clinical practice setting is the essential next step to confirm the clinical reliability and potential utility of the F-PAR tool. Such studies are already ongoing.

In summary, the Delphi Survey reported in this paper provided a rapid and robust route to obtaining a credible and clinically relevant definition of F-PAR in CC. The definition obtained is worded in a way which will make it easy to use as a clinical check list or clinical decision support tool when determining if a treatment for CC should be changed, or if a patient with CC should be referred for investigation in secondary care.

**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Round 1 results. (a) Proposition framed as a question to the patient with their answer. (b) Propositions made as statements.

**Figure S1.** Round 1 results showing severity vs. median panel rating on Likert scale (4 & 5 = F-PAR) with results ordered by severity within themes.

**AUTHORSHIP**

**Guarantor of the article:** Anton Emmanuel MD.

**Author contributions:** Hugh Boardman MD wrote the initial draft of the manuscript, Jan Tack MD, Peter Layer MD, Ingolf Schiefke MD, David Jayne MD, Hugh Boardman MD, and Anton Emmanuel MD collaborated in the interpretation of data. All of the authors provided critical revision of the manuscript and contributed their expert opinions by completing the Delphi questionnaires from which the raw data used to build the Delphi consensus were obtained.

All authors approved the final version of the manuscript.

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APPENDIX 1
CLINICAL EXPERT PARTICIPANTS AND THEIR COMPLETE AFFILIATIONS

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