

RESEARCH ARTICLE

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A rapid, simple questionnaire to assess gastrointestinal symptoms after oral ferrous sulphate supplementation

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Abstract

Background: Oral iron supplementation is often associated with rapid onset of gastrointestinal side-effects. The aim of this study was to develop and trial a short, simple questionnaire to capture these early side-effects and to determine which symptoms are more discriminating.

Methods: The study was a double-blind placebo-controlled randomized parallel trial with one week treatment followed by one week wash-out. Subjects were randomized into two treatment groups ($n = 10/\text{group}$) to receive either ferrous sulphate (200 mg capsules containing 65 mg of iron) or placebo, both to be taken at mealtimes twice daily during the treatment period. Subjects completed the questionnaires daily for 14 days. The questionnaire included gastrointestinal symptoms commonly reported to be associated with the oral intake of ferrous iron salts (i.e. nausea, vomiting, heartburn, abdominal pain, diarrhoea, and constipation).

Results: Seventy five per cent of participants reporting the presence of one or more symptoms in the first week of the study were in the ferrous sulphate group. In the second week of the study (i.e. wash-out), 67% of the participants reporting one or more symptom(s) were in the ferrous sulphate group. In the first week of the study (treatment) the number of symptoms reported by participants in the ferrous sulphate group (mean \pm SEM = 6.7 ± 1.7) was significantly higher than that for participants in the placebo group (1.2 ± 0.5) ($p = 0.01$). In the second week of the study (wash-out) the number of symptoms reported by participants in the ferrous sulphate group (4.6 ± 2.0) appeared higher than for participants in the placebo group (1.0 ± 0.7) although this did not reach significance ($p = 0.12$). Events for which the gastrointestinal symptom questionnaire was most discriminatory between ferrous sulphate and placebo groups were: heartburn, abdominal pain and the presence of black stools (all $p \leq 0.03$).

Conclusions: A tool for the detection of commonly-occurring side effects should not require large study numbers to be effective. With just 10 subjects per group (iron or placebo), this simple questionnaire measures gastrointestinal side-effects associated with oral iron (ferrous sulphate) supplementation, and would be appropriate for use in intervention studies or clinical trials.

Trial registration: ClinicalTrials.gov Identifier: NCT02146053 (21/05/2014).

Keywords: Gastrointestinal symptoms, Ferrous sulphate, Iron supplementation, Side-effects, Adverse events, Oral iron

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Background

Despite many attempts to eradicate or even reduce iron deficiency anaemia (IDA), it remains the most prevalent nutritional deficiency disorder in the world affecting around 1.1 billion people of which nearly 400 million are children. The World Health Organization (WHO) reports that worldwide, at any given moment, more individuals have IDA than any other health problem [1]. Iron deficiency anaemia accounts for 2.4% of the global disease burden and it occupies the World Health Organization (WHO) top ten hit list of targeted global health problems [1-3].

One of the hurdles to eradicate this disorder has been the use of iron preparations, typically ferrous iron salts 65 mg_{Fe} 2–3 times daily [4], that risk significant gastrointestinal disturbances [5-10] and systemic infection [11-14]. Data from the National Health Service shows that at least 97.5% of the prescriptions filled for oral iron in England alone are for simple ferrous salts (sulphate, fumarate or gluconate) [15]. In the main, gastrointestinal side-effects start to present early in the treatment course [7,16,17] albeit onset of symptoms and severity must be related to the

iron dosage and the posology followed (i.e. weekly or daily) [18-23]. Reasons for gastrointestinal disturbance are well described: even in subjects with IDA only about 20-30% of oral supplemented iron is absorbed, while the remainder transits through the gut lumen inducing (a) free radical mediated damage to the gut mucosa [9,24-26] and (b) undesirable changes to colonic microflora [27-29]. Gastrointestinal symptoms impact on the general wellbeing of individuals [30-37] and are known to affect compliance with oral iron therapy and, therefore, treatment efficacy [7,19,38-40].

Self-reporting questionnaires may be used to monitor gastrointestinal symptoms in disease-specific scenarios [35,41-44], although only a few have been formally tested [36], but there is currently no gastrointestinal-specific questionnaire to identify oral iron-induced symptoms in healthy subjects [45]. The current study presents a simple one-page gastrointestinal symptom questionnaire (a) to capture the early side-effects normally associated with oral iron (ferrous sulphate) supplementation and (b) to determine which symptoms are more discriminant. Since

ID CODE _____ WEEK _____ DAY _____

A How is your general health today? (Please tick one box)

Very Good Good Fair Poor

B How does this compare to yesterday? (Please tick one box)

Better The same Worse Much worse

C Please record any symptoms you may have had today (tick one box for each symptom experienced)

Absent I did not have this symptom at all
 Mild I had this symptom occasionally, but it did not really bother me
 Moderate I had this symptom often, it bothered me quite a bit
 Severe I had this symptom very often, it bothered me a great deal

	Absent	Mild	Moderate	Severe
Have you felt any nausea (wanting to vomit) today?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you actually vomited today?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you had heartburn (burning in chest) today?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you had abdominal pain today?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you had a headache today?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you been breathless today?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you had diarrhoea today?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Have you had constipation today?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

D If you experienced the following symptoms how would you describe the intensity? (Please tick one box for each symptom experienced)

	Mild	Moderate	Severe
Nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Heartburn	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Abdominal pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

E If you experienced the symptoms below how would you describe the inconvenience? (Please tick one box for each symptom experienced)

	Mild	Moderate	Severe
Nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Heartburn	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Abdominal pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

F How long did the following symptoms last today?

Nausea	<input type="checkbox"/> <input type="checkbox"/> hours <input type="checkbox"/> <input type="checkbox"/> minutes
Heartburn	<input type="checkbox"/> <input type="checkbox"/> hours <input type="checkbox"/> <input type="checkbox"/> minutes
Abdominal pain	<input type="checkbox"/> <input type="checkbox"/> hours <input type="checkbox"/> <input type="checkbox"/> minutes

G How many times did the following symptoms occur today? (Specify)

Nausea	<input type="checkbox"/> <input type="checkbox"/>
Heartburn	<input type="checkbox"/> <input type="checkbox"/>
Abdominal pain	<input type="checkbox"/> <input type="checkbox"/>

H How many bowel movements have you had today? (Specify)
 Is this normal for you? Yes No
 How many of your bowel movements were black? (Specify)

I Did you take your tablets today? (If yes, please tick box)
 Morning Evening
 If you did not take either of your tablets, please explain why

J Are your symptoms likely to be related to taking your study tablets
 If no, please describe why Yes No

Figure 1 One-page symptom questionnaire to assess gastrointestinal adverse effects after oral iron supplementation. The letters 'A' to 'J' are not present on the actual questionnaire but are herein shown for ease of reference throughout this manuscript.

Table 1 Baseline socio-demographic data for the participants in the 2 study groups

	Iron group (n = 10)	Placebo group (n = 10)
Age (years)		
Mean (SD)	32.2 (10.4)	31.7 (10.8)
Range	21-58	22-59
Gender [n]		
Male	3	4
Female	7	6
Highest education level [n (%)]		
GCSE	1 (10)	0
A level	2 (20)	4 (40)
First degree or professional qualification	4 (40)	3 (30)
Higher degree	3 (30)	3 (30)
Job title [n (%)]		
Undergraduate student	4 (40)	3 (30)
PhD student	2 (20)	1 (10)
Secretary	1 (10)	0
Retired teacher	0	1 (10)
Dietician	3 (30)	2 (20)
Research fellow	0	2 (20)
Clinician	0	1 (10)

Differences were not significant between the 2 groups, with $p > 0.05$.

gastrointestinal side effects, following oral iron, are reportedly so common, any robust questionnaire should be valid in just a small number of subjects. With just 10 subjects per group (iron or placebo), this questionnaire is shown to be a useful instrument to measure gastrointestinal side-effects associated with oral iron supplementation, and would thus be appropriate for use in intervention studies or clinical trials.

Methods

Gastrointestinal symptom questionnaire

Questions for the gastrointestinal symptom questionnaire (Figure 1) were based on previously validated bowel symptom questionnaires [30,44,46,47] and included gastrointestinal symptoms commonly reported to be associated with the oral intake of ferrous iron salts: i.e. nausea, vomiting, heartburn, abdominal pain, diarrhoea, and constipation [5,19,48,49]. In addition, the questionnaire included questions on breathlessness because this is common in anaemic patients and headache that, although not generally associated with oral iron therapy, is common with some gastrointestinal complaints [50,51].

The degree of discomfort from each symptom was ranked by the study subjects in one of four categories

(absent, mild, moderate or severe) as used in previous studies [44,52]. The frequency of bowel movements was registered and the questionnaire included a question on whether these were normal or abnormal. Compliance with the oral iron or placebo treatment was also assessed.

Participants

Twenty healthy subjects, seven men and thirteen women aged 18–65 years (average age 32), were recruited via circular email. The presence of any chronic disease, pregnancy or lactation were considered as exclusion criteria. Subjects were asked to complete a baseline questionnaire including demographic questions on age, gender, education and job title.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the King's College London (KCL) Research Ethics Committee and treatment capsules were approved by the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA). Written informed consent was obtained from all subjects.

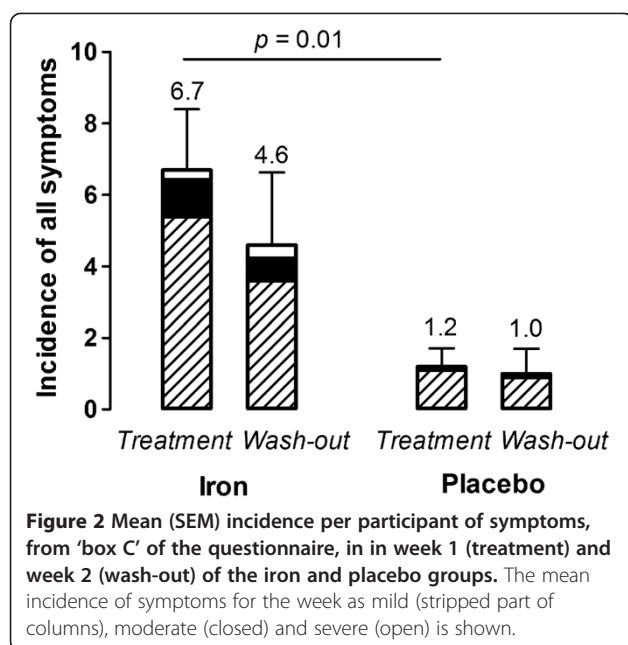
Study design

The study was a double-blind placebo-controlled randomized parallel trial with one week treatment followed by one week wash-out. Subjects were randomised into two treatment groups (n = 10/group) to receive either ferrous sulphate (200 mg capsules containing 65 mg of iron) or placebo, both to be taken at mealtimes twice daily for 7 days during the treatment period. All subjects were advised that they may suffer black stools, as a normal consequence of intervention, irrespective of whether they were on placebo or oral iron (although placebo had no specific stool-darkener added).

Subjects were provided with two seven-day symptom questionnaires (Figure 1) to take home for self-completion, and asked to complete them on a daily basis for 14 days – the first 7 days whilst on one of the treatments (i.e. ferrous sulphate or placebo) and the following 7 days during the respective wash-out periods. The symptom diaries were coded and anonymised. Codes were broken only after the raw questionnaire data had been entered into the database.

Data analysis

The questionnaire is broken down into different compartments (boxes 'A'-'J') for ease of reference in this manuscript (Figure 1). Although all data were collected, only those from boxes C, H,I and J were analysed and are herein reported in figures, tables and/or text. All statistical analysis was performed using GraphPad Prism version 5.03 for Windows (GraphPad Software, San Diego, California, USA). Results are presented as means with either standard error of mean (SEM) or standard deviation (SD) as



described. Unless otherwise stated, differences between treatment and wash-out periods and between ferrous sulphate and placebo were examined using the unpaired *t*-test (two-tailed) with Welch's correction for non-equal variances (level of significance set to $p < 0.05$). Where, for the

placebo group, there was an absence of an individual symptom (i.e. for heartburn, breathlessness or black stools) comparisons with the ferrous sulphate group were made using the paired *t*-test (two-tailed). The number of black stool movements on each day was compared using the one-way analysis of variance with the Bonferroni post-hoc test to correct for multiple comparisons.

Results and discussion

Twenty healthy subjects (10/group) took part in the study. The two study groups were similar in terms of socio-demographic characteristics, age and gender (Table 1). Participants were randomly allocated to the 2 groups (ferrous sulphate or placebo) and asked to complete the gastrointestinal symptom questionnaire every day for 14 days. The completion rate of the symptom questionnaire was 100%. All participants found the symptom questionnaire easy to complete but some suggested that a 'comments' section be included so that they could, at times, provide reasons for responses. The average time for completion of the questionnaire was less than 5 minutes per day. Compliance with oral iron/placebo was >80% for the morning dose and >90% for the evening dose for participants in both groups and did not differ between groups. Reasons provided for non-compliance were unrelated to the study treatments.

Table 2 Frequency of individual symptoms irrespective of whether mild, moderate or severe (days per week)

Symptom	Iron		Placebo		<i>p</i> value [#]
	Treatment	Wash-out	Treatment	Wash-out	
Nausea	1.1 ± 0.6 (-0.3; 2.5)	0.1 ± 0.1 (-0.1; 0.3)	0.2 ± 0.1 (-0.1; 0.5)	0.4 ± 0.4 (-0.5; 1.3)	0.2
Heartburn	1.0 ± 0.4 (0.1; 1.9)	0.3 ± 0.3 (-0.4; 1.0)	0 (0; 0)	0 (0; 0)	0.03
Abdominal pain	2.0 ± 0.6 (0.5; 3.5)	1.0 ± 0.7 (-0.7; 2.7)	0.2 ± 0.1 (-0.1; 0.5)	0 (0; 0)	0.02
Headache	1.1 ± 0.5 (-0.1; 2.3)	1.6 ± 0.6 (0.2; 3.0)	0.2 ± 0.2 (-0.3; 0.7)	0.1 ± 0.1 (-0.1; 0.3)	0.15
Breathlessness	0.1 ± 0.1 (-0.1; 0.3)	0.5 ± 0.3 (-0.3; 1.3)	0 (0; 0)	0.1 ± 0.1 (-0.1; 0.3)	0.3
Diarrhoea	0.4 ± 0.3 (-0.3; 1.1)	0.3 ± 0.2 (-0.2; 0.8)	0.3 ± 0.3 (-0.4; 1.0)	0.4 ± 0.2 (-0.1; 0.9)	0.8
Constipation	1.0 ± 0.6 (-0.3; 2.3)	0.7 ± 0.5 (-0.4; 1.8)	0.2 ± 0.2 (-0.3; 0.7)	0 (0; 0)	0.2
Change bowel movements	1.3 ± 0.5 (0.1; 2.5)	1.5 ± 0.3 (0.7; 2.3)	0.4 ± 0.3 (-0.2; 1.0)	0.4 ± 0.2 (-0.1; 0.9)	0.15
Black stools	4.1 ± 0.7 (2.4; 5.8)	1.3 ± 0.4 (0.4; 2.2)	0 (0; 0)	0 (0; 0)	0.0004

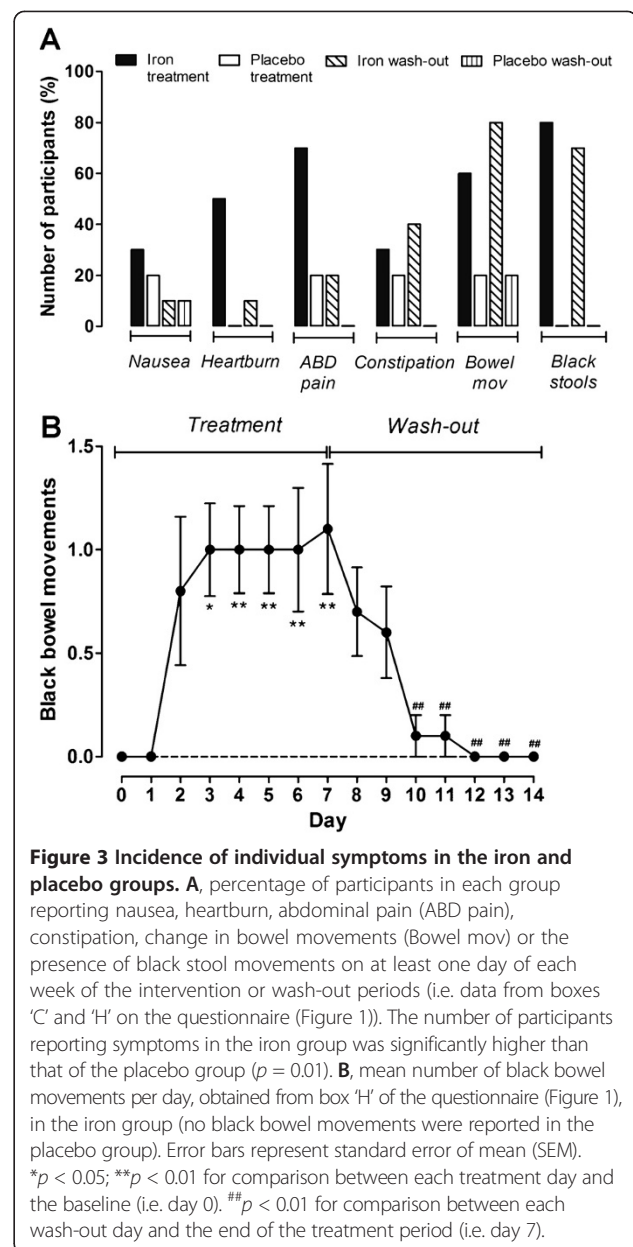
$p = 0.002$

Values, derived from boxes 'C' and 'H' of the questionnaire (Figure 1), are shown as mean ± standard error (95% confidence interval) for the two groups. [#]significance value ($p < 0.05$) between the frequency of each symptom for the Iron treatment period versus the Placebo treatment period.

In summary, a total of 12 (out of 20) participants reported the presence of one or more symptom(s) in the first week of the study (i.e. during treatment), of which 9 (75%) were in the ferrous sulphate group. In the second week of the study (i.e. wash-out), 9 participants reported one or more symptom(s), of which 6 (67%) were in the ferrous sulphate group. The degree of discomfort caused by each symptom was categorised into mild, moderate or severe as defined in box 'C' of the questionnaire (Figure 1). Detailed analyses were as follows: in the first week of the study (treatment) the number of symptoms reported per participant in the ferrous sulphate group (mean = 6.7, SEM = 1.7) was significantly higher than that reported per participant in the placebo group (mean = 1.2, SEM = 0.5) ($p = 0.01$). In the second week of the study (wash-out) the number of symptoms reported per participant in the ferrous sulphate group (mean = 4.6, SEM = 2.0) tended to be higher than that per participant in the placebo group (mean = 1.0, SEM = 0.7) but this did not reach significance ($p = 0.12$) (Figure 2).

Table 2 shows the reported frequency for individual symptoms by the participants in the ferrous sulphate and placebo groups during the treatment and wash-out periods. Adverse events for which the gastrointestinal symptom questionnaire was most discriminatory between ferrous sulphate and placebo groups were: heartburn, abdominal pain and the presence of black stools (all $p \leq 0.03$) (Table 2). The differences observed in nausea, constipation and change in bowel movements between the ferrous sulphate and placebo groups may be clinically significant but, due to the small sample size, did not reach statistical significance (Table 2). The number of participants in each group reporting these individual symptoms is presented in Figure 3A, for both treatment and wash-out weeks. Vomiting was not reported by participants in either group on any day. Overall, the number of participants reporting symptoms in the iron group was significantly higher than the number of participants reporting symptoms in the placebo group ($p = 0.01$). The nature of the symptoms reported in the oral iron group is not surprising as iron that remains soluble in the intestinal lumen is likely to be bioavailable but, equally, may be available for other processes including uptake by commensal flora and colonic epithelial cells, and facile redox-cycling in the gut lumen. Indeed, the generation of harmful free-radicals through Fenton chemistry which can cause inflammation and oxidative stress in the intestinal mucosa has been linked to available luminal iron in several studies [53-55]. Furthermore, detrimental changes to the commensal microbiota have recently been reported with oral iron supplementation and may be partly responsible for the distal symptoms such as constipation and diarrhoea [27-29,56].

Figure 3B shows the number of black stool movements reported in the ferrous sulphate group: no black stools



were reported by participants in the placebo group. For those participants taking ferrous sulphate there was a significant increase in the number of black stool movements from day 3 of the treatment period ($p = 0.03$) which only returned to baseline 3 days after stopping the ferrous sulphate tablets (i.e. day 10 of the study) ($p = 0.005$) (Figure 3B). Although subjects were not aware of which group they were in (i.e. treatment or placebo), the presence of black stools could have provided an indication of their randomisation to oral iron. It is thus important to note that symptoms were being reported in the ferrous sulphate group from the first day (for example nausea and abdominal pain) and this was before the onset of black stools which was significant at 72 hours.

The blackening of stools following oral iron supplementation is derived from the reaction of hydrogen sulphide produced by commensal bacteria, such as sulphate-reducing bacteria, with ferrous iron (Fe^{2+}) to produce iron sulphide (FeS). Sulphate-reducing bacteria are a group of 'emerging pathogens' in the colon. These bacteria have an exceptionally high requirement for iron and use sulphur or sulphate, which are plentiful in the colon from the digestion of foods, as electron acceptors during anaerobic respiration, for the oxidative metabolism of organic compounds and H_2 [57]. Indeed, Werner et al. have shown that numbers of *Desulfovibrio* (the main sulphate-reducing bacteria found in faeces) significantly increased following ferrous sulphate supplementation [28].

Conclusions

A short and simple-to-answer gastrointestinal symptom questionnaire was developed as a tool to measure adverse-effects for use in intervention studies with oral iron and especially when ferrous sulphate comprises one study arm. The present small study aimed to show where the questionnaire had discriminatory power: i.e. which symptoms are more sensitive to oral ferrous sulphate therapy. The questionnaire was filled in by the study participants during the 7-days of the treatment period and the 7-days of the wash-out period and was discriminant in the total number of reported symptoms per participant between the iron and the placebo groups. Additionally, it showed that the individual symptoms that were significantly more sensitive to the oral iron treatment were heartburn, abdominal pain and the presence of black stools. Although there has been concern that black stools caused by oral iron may mask black stools caused by gastrointestinal blood loss, it is not per se an adverse-effect related to symptoms but, rather, it represents the formation of iron sulphide in the colon due to bacterial activity. However, it could be useful as a marker of the change in bacterial flora (i.e. an increase in sulphate-reducing bacteria at the expense of beneficial bacterial genus such as lactobacilli) in future intervention studies with oral iron and this could be further investigated.

Despite the uncomplicated format of the questionnaire, a large amount of data is generated. For example, in this small study, 20 participants provided 14 days of questionnaire each (i.e. 280 questionnaires) with 28 pieces of information per questionnaire: this represents 7,840 pieces of data recorded, for most, in a categorical format, for some in a binary form, and for others in a continuous format.

To facilitate analysis, the main outcomes were restricted to binary events (e.g. presence and absence of symptoms), and the categorisation of their severity was only focussed on data collected from boxes C, H and I of the questionnaire. Clearly, in future studies that utilise this questionnaire, researchers will need to determine whether (a) they collect all data or simplify the questionnaire even further

so that only C, H and I are used and (b) if they collect all, how it should be best analysed.

Finally, whether the whole questionnaire (Figure 1) is used, or a short version with only boxes C, H and I, a comments box may be a useful addition for patients/participants to provide detail that may inform upon their responses.

Competing interests

The authors declare no conflict of interest but DIAP and JJP wish to note that they are co-inventors on a patent detailing novel Fe(III) poly oxo-hydroxide structures that may have potential as dietary supplements and that they consult to Iron Therapeutics UK Limited for advice on their novel oral iron therapeutic.

Authors' contributions

MCEL and JJP designed the research; MCEL conducted the research; DIAP and SMI analysed data; DIAP, SMI and JJP wrote the paper; DIAP and JJP had primary responsibility for final content. All authors read and approved the final manuscript.

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