



Clinical trial results:

TREATMENT OF IRON DEFICIENCY ANAEMIA IN ADOLESCENTS WITH INFLAMMATORY BOWEL DISEASE USING FERROUS SULPHATE OR COSMOFER: TOLERANCE AND EFFECTS ON HAEMOGLOBIN, DISEASE ACTIVITY, MOOD, QUALITY OF LIFE AND AUTONOMIC NERVOUS SYSTEM ACTIVITY. AN OPEN LABEL PHASE IV NON-INFERIORITY STUDY.

Summary

EudraCT number	2010-023797-39
Trial protocol	GB
Global end of trial date	20 August 2015

Results information

Result version number	v1 (current)
This version publication date	26 April 2017
First version publication date	26 April 2017
Summary attachment (see zip file)	End of Trial report (End of Trial Report DSR 2017.docx) Oral iron treatment response (Final DSR JCC paper Oral Iron Treatment Response.pdf)

Trial information

Trial identification

Sponsor protocol code	v.2 21 July 2015
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01991314
WHO universal trial number (UTN)	-
Other trial identifiers	CSP ref: 40738, EudraCT number: 2010-023797-39, REDA ref: 007495BLT, REC ref: 10/H0504/90

Notes:

Sponsors

Sponsor organisation name	Barts Health NHS Trust
Sponsor organisation address	Joint Research Management Office, QM Innovations Building, 5 Walden Street , London, United Kingdom, E12EF
Public contact	Marie-Claire Rickard, Joint Research Management Office, +44 2078827272, m.rickard@qmul.ac.uk
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No
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Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 May 2015
Global end of trial reached?	Yes
Global end of trial date	20 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess these hypotheses:

- [1] there is no difference in the haemoglobin response to oral iron treatment of iron deficiency anaemia (IDA) in adolescent compared to adult IBD patients;
- [2] oral iron does not worsen disease activity in IBD;
- [3] response to oral iron is inversely related to serum hepcidin concentrations at baseline; and
- [4] treatment of anaemia improves QOL, mood and fatigue in adolescent and adult patients with IBD.

Protection of trial subjects:

Patients were fully informed of the aims of the trial verbally and with patient information sheets. Their usual outpatient care was undertaken (including routine blood samples before and after treatment with oral iron), the only extra procedures being collection of two stool samples (for measurement of faecal calprotectin) and completion of psychometric questionnaires. There was no pain or distress involved.

Background therapy:

Patients were on a range of treatments for their inflammatory bowel disease (IBD). These are shown in Table 1 of the attached paper and were, in adolescents and adults respectively, the following: 5 ASA 32 [71%], 17 [40%]; prednisolone/budesonide 7 [16%], 7 [16%]; enteral nutrition 3 [7%], 0 [0%]; thiopurine 23 [51%], 20 [47%]; methotrexate or ciclosporine 2 [4%], 0 [0%]; anti-TNF 2 [4%], 3 [7%]; antidepressants 0 [0%], 3 [7%].

Evidence for comparator:

Iron deficiency anaemia [IDA] is a frequent complication of IBD. In children and adolescents IDA appears to be commoner than in adults and is often undertreated, perhaps reflecting paediatricians' concerns about side effects, including worsening of disease activity, and about young people's medication adherence. Quality of life [QOL] correlates negatively with severity of anaemia in IBD. Prospective studies of oral and intravenous iron in adults with IBD have shown improvements in QOL when the haemoglobin [Hb] is corrected but this effect has not been assessed in young people with IBD. Psychological distress and fatigue are common in people of all ages with IBD but to our knowledge there have been no prospective studies of the effects of oral iron supplementation on these factors in people with IBD.

It is widely stated that the Hb response to oral iron is reduced in patients with active IBD: this has been confirmed in one but not all studies. Such an effect could be explained by involvement of hepcidin, which regulates iron homeostasis by inhibiting its uptake by enterocytes, macrophages and hepatocytes. Serum hepcidin levels are increased by pro-inflammatory cytokines; conversely, in iron deficiency, hepcidin levels fall. Serum hepcidin concentrations at baseline are related inversely to the Hb response to oral iron in patients with rheumatoid arthritis and other diseases, but whether this is true in IBD is unknown.

We therefore undertook a prospective phase IV, open-label, parallel group, 6-week non-inferiority clinical trial using oral ferrous sulphate to assess the hypotheses that: [1] there is no difference in the Hb response to oral iron treatment of IDA in adolescent compared to adult IBD patients; [2] oral iron does not worsen disease activity in IBD; [3] response to oral iron is inversely to serum hepcidin concentrations at baseline; and [4] treatment of anaemia improves QOL, mood and fatigue in these patients

Actual start date of recruitment	04 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 88
Worldwide total number of subjects	88
EEA total number of subjects	88

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	41
Adults (18-64 years)	46
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between January 2012 and April 2015, adolescent and adult patients with IBD (ulcerative colitis, Crohn's disease or IBD unclassified) were recruited at Barts and the Royal London Hospitals, Barts Health Trust or at Chelsea and Westminster Hospital, London , UK.

Pre-assignment

Screening details:

Patients who within the next month were due to attend the adult, young people's and paediatric IBD clinics were screened for the result of their haemoglobin concentration at their previous clinic attendance. Those found to be anaemic were sent a letter of explanation about, and invitation to participate in the trial.

Period 1

Period 1 title	Patients at baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
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Arm title	Adolescents aged 13-18 years
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Arm description:

Adolescents with IBD and IDA

Arm type	Active comparator
Investigational medicinal product name	Ferrous sulphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200mg twice daily for 6 weeks

Arm title	Adults aged 19 or more
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Arm description:

Adults aged 19 or more with IBD and IDA

Arm type	Active comparator
Investigational medicinal product name	Ferrous sulphate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200mg twice daily for 6 weeks

Number of subjects in period 1	Adolescents aged 13-18 years	Adults aged 19 or more
Started	45	43
Completed	34	32
Not completed	11	11
Adverse event, non-fatal	5	1
Lost to follow-up	6	10

Baseline characteristics

Reporting groups

Reporting group title	Adolescents aged 13-18 years
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Reporting group description:

Adolescents with IBD and IDA

Reporting group title	Adults aged 19 or more
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Reporting group description:

Adults aged 19 or more with IBD and IDA

Reporting group values	Adolescents aged 13-18 years	Adults aged 19 or more	Total
Number of subjects	45	43	88
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	14.9	32.5	-
standard deviation	± 1.67	± 11.4	-
Gender categorical			
Units: Subjects			
Female	22	23	45
Male	23	20	43
Haemoglobin			
Units: g/dl			
arithmetic mean	10.3	10.9	-
standard deviation	± 1.21	± 2.23	-
Serum hepcidin			
Units: ng/ml			
arithmetic mean	31.3	28.7	-
standard deviation	± 26.2	± 19	-
transferrin saturation			
Units: percent weight/weight			
arithmetic mean	7	7.8	-
standard deviation	± 2.4	± 3.9	-
C-reactive protein			
Units: mg/l			
arithmetic mean	9.9	11.4	-
standard deviation	± 22.8	± 19	-
Faecal calprotectin			
Units: ug/g			
arithmetic mean	295	299	-
standard deviation	± 322	± 511	-
Shortened IBD Questionnaire			
Quality of life questionnaire validated for patients with IBD			
Units: numbers			
arithmetic mean	51	44	-
standard deviation	± 12.7	± 15.1	-

HADS-A			
Hospital anxiety and depression score - anxiety			
Units: numbers			
arithmetic mean	7.3	8.1	
standard deviation	± 5.4	± 4.6	-
HADS-D			
HADS-depression			
Units: numbers			
arithmetic mean	4.4	6	
standard deviation	± 4	± 3.9	-
Perceived Stress Questionnaire-G			
Assessment of perceived stress			
Units: numbers			
arithmetic mean	57	71	
standard deviation	± 15.4	± 15.7	-
Multidimensional Fatigue Inventory			
Measure of fatigue			
Units: numbers			
arithmetic mean	58	60	
standard deviation	± 7.5	± 7.2	-

End points

End points reporting groups

Reporting group title	Adolescents aged 13-18 years
Reporting group description: Adolescents with IBD and IDA	
Reporting group title	Adults aged 19 or more
Reporting group description: Adults aged 19 or more with IBD and IDA	

Primary: Increase in haemoglobin concentration (1)

End point title	Increase in haemoglobin concentration (1)
End point description: Intention to treat analysis	
End point type	Primary
End point timeframe: after 6 weeks on ferrous sulphate	

End point values	Adolescents aged 13-18 years	Adults aged 19 or more		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	43		
Units: g/dl				
arithmetic mean (confidence interval 95%)	1.22 (0.79 to 1.64)	1.3 (0.84 to 1.75)		

Statistical analyses

Statistical analysis title	ANCOVA
Statistical analysis description: To test the hypothesis of non-inferiority with maximal statistical power, ANCOVA was used to compare the change in mean haemoglobin levels between adults and adolescents after accounting for necessary covariates. 95% confidence intervals were established for the treatment effects to determine the status of the primary hypothesis.	
Comparison groups	Adolescents aged 13-18 years v Adults aged 19 or more
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8
Method	ANCOVA
Parameter estimate	Mean difference (net)

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
Variability estimate	Standard deviation
Dispersion value	0.7

Primary: Increase in haemoglobin concentration (2)

End point title	Increase in haemoglobin concentration (2)
End point description:	
End point type	Primary
End point timeframe:	
6 weeks	

End point values	Adolescents aged 13-18 years	Adults aged 19 or more		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	43		
Units: g/dl				
arithmetic mean (standard deviation)	1.4 (± 1.5)	1 (± 1.5)		

Statistical analyses

Statistical analysis title	Student's t test (unpaired)
Statistical analysis description:	
To compare the change in Hb produced by oral iron between the adolescent and adult groups	
Comparison groups	Adolescents aged 13-18 years v Adults aged 19 or more
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.23
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)

Notes:

[1] - See above. Statistical Package for the Social Sciences [SPSS] [version 16] was used for the statistical analysis.

Primary: Numbers of patients normalising haemoglobin

End point title	Numbers of patients normalising haemoglobin
End point description:	
Using the chi-squared test, we compared the proportions of patients in each group in whom ferrous sulphate produced a normalisation of haemoglobin concentration by WHO criteria	
End point type	Primary

End point timeframe:

6 weeks

End point values	Adolescents aged 13-18 years	Adults aged 19 or more		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	43		
Units: numbers				
number (not applicable)	13	16		

Statistical analyses

Statistical analysis title	Chi squared test
Comparison groups	Adolescents aged 13-18 years v Adults aged 19 or more
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	Chi-squared

Secondary: Increase in serum hepcidin concentration

End point title	Increase in serum hepcidin concentration
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Adolescents aged 13-18 years	Adults aged 19 or more		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	43		
Units: ng/ml				
arithmetic mean (standard error)	4.8 ($\pm$ 2.4)	6.6 ($\pm$ 2.6)		

Statistical analyses

Statistical analysis title	Unpaired Student's t test
Comparison groups	Adolescents aged 13-18 years v Adults aged 19 or more
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.6
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)

Notes:

[2] - This test was to see if there was a difference in hepcidin response to oral iron between the two arms.

Secondary: Increase in transferrin saturation

End point title	Increase in transferrin saturation
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Adolescents aged 13-18 years	Adults aged 19 or more		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	43		
Units: percentage				
arithmetic mean (standard error)	10.5 (± 2.3)	10.7 (± 2.2)		

Statistical analyses

Statistical analysis title	Unpaired Student's t test
Comparison groups	Adolescents aged 13-18 years v Adults aged 19 or more
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)

Secondary: Change in C reactive protein

End point title	Change in C reactive protein
End point description:	
End point type	Secondary

End point timeframe:

6 weeks

End point values	Adolescents aged 13-18 years	Adults aged 19 or more		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	32		
Units: mg/l				
arithmetic mean (standard error)	0.5 ($\pm$ 1.5)	1.5 ($\pm$ 3.4)		

Statistical analyses

Statistical analysis title	Unpaired Student's t test
Comparison groups	Adolescents aged 13-18 years v Adults aged 19 or more
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	t-test, 2-sided

Secondary: Change in faecal calprotectin

End point title	Change in faecal calprotectin
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Adolescents aged 13-18 years	Adults aged 19 or more		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	32		
Units: ug/g				
arithmetic mean (standard error)	-35 ($\pm$ 38)	-40 ($\pm$ 81)		

Statistical analyses

Statistical analysis title	Unpaired Student's t test
Comparison groups	Adolescents aged 13-18 years v Adults aged 19 or more
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96
Method	t-test, 2-sided

Secondary: Change in SIBDQ

End point title	Change in SIBDQ
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Adolescents aged 13-18 years	Adults aged 19 or more		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	32		
Units: numbers				
arithmetic mean (standard error)	3.2 (± 2.6)	5.7 (± 2)		

Statistical analyses

Statistical analysis title	Unpaired Student's t test
Comparison groups	Adolescents aged 13-18 years v Adults aged 19 or more
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.49
Method	t-test, 2-sided

Secondary: Change in HADS-A

End point title	Change in HADS-A
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Adolescents aged 13-18 years	Adults aged 19 or more		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	32		
Units: numbers				
arithmetic mean (standard error)	-0.7 ($\pm$ 0.5)	-1.1 ($\pm$ 0.7)		

Statistical analyses

Statistical analysis title	Unpaired Student's t test
Comparison groups	Adolescents aged 13-18 years v Adults aged 19 or more
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85
Method	t-test, 2-sided

Secondary: Change in HADS-D

End point title	Change in HADS-D
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Adolescents aged 13-18 years	Adults aged 19 or more		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	32		
Units: numbers				
arithmetic mean (standard error)	-0.5 ($\pm$ 0.5)	-0.9 ($\pm$ 0.7)		

Statistical analyses

Statistical analysis title	Unpaired Student's t test
Comparison groups	Adolescents aged 13-18 years v Adults aged 19 or more

Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	t-test, 2-sided

Secondary: Change in PSQ-G

End point title	Change in PSQ-G
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Adolescents aged 13-18 years	Adults aged 19 or more		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	32		
Units: numbers				
arithmetic mean (standard error)	4.1 ($\pm$ 2.5)	-11.8 ($\pm$ 2.5)		

Statistical analyses

Statistical analysis title	Unpaired Student's t test
Comparison groups	Adolescents aged 13-18 years v Adults aged 19 or more
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided

Secondary: Change in MFI

End point title	Change in MFI
End point description:	
End point type	Secondary
End point timeframe:	
6 weeks	

End point values	Adolescents aged 13-18 years	Adults aged 19 or more		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	32		
Units: numbers				
arithmetic mean (standard error)	0.9 ($\pm$ 1.4)	1.9 ($\pm$ 0.7)		

Statistical analyses

Statistical analysis title	Unpaired Student's t test
Comparison groups	Adolescents aged 13-18 years v Adults aged 19 or more
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 weeks

Assessment type	Non-systematic
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Dictionary used

Dictionary name	SNOMED CT
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Dictionary version	1
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Reporting groups

Reporting group title	Adolescents
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Reporting group description:

Adolescents aged 13-18

Reporting group title	Adults aged 19 or more
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Reporting group description: -

Serious adverse events	Adolescents	Adults aged 19 or more	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 45 (4.44%)	1 / 43 (2.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abdominal pain	Additional description: Also vomiting and constipation		
subjects affected / exposed	2 / 45 (4.44%)	0 / 43 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative	Additional description: Relapse of her ulcerative colitis as her steroid dose was reduced		
subjects affected / exposed	0 / 45 (0.00%)	1 / 43 (2.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Adolescents	Adults aged 19 or more	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 45 (17.78%)	7 / 43 (16.28%)	
Nervous system disorders			

Headache subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1	0 / 43 (0.00%) 0	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	4 / 45 (8.89%) 4	4 / 43 (9.30%) 4	
Nausea	Additional description: with vomiting		
subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2	0 / 43 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	0 / 45 (0.00%) 0	3 / 43 (6.98%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2012	Because of staffing reductions, we reduced the numbers of investigations (nutritional assessment, exercise tolerance testing and Neuroscope testing) which we had planned in the original version of the Protocol; in addition, we decided that we were no longer able to provide Cosmofer in the necessary time-frame for the patients who proved to be intolerant of oral ferrous sulphate.
14 September 2012	1. We requested an increase in the number of patients to be approached for recruitment from 90 to 140, because a higher than expected number of patients had turned out not to meet the inclusion criteria at the time of planned recruitment because their post-consent blood test showed them either to be no longer anaemic by WHO standards, or no longer iron deficient (Fe saturation <18%) (ie, during the time between their previous out-patient appointment and the intended recruitment date, their haemoglobin and iron status had improved). 2. Because of Pharmacy staffing shortages, to save time and inconvenience for patients attending afternoon clinics at the Royal London or any clinics at St Bartholomew's Hospital, we arranged for prescriptions for ferrous sulphate to be collected from the Pharmacy at the Royal London by one of the investigators before the potential participants attended the clinic to give their written consent, giving them their tablets if/when this was been obtained.
21 January 2013	Change of name of sponsor from Barts and the London NHS Trust to Barts Health NHS Trust
24 January 2013	Because the initial suppliers, Wockhardt Ltd, could no longer make or supply ferrous sulphate tablets, we had to obtain them from an alternative supplier, Teva UK Ltd.
10 October 2013	1. Because of staff changes, we altered the arrangements for obtaining and countersigning patients' consent. Consent was taken by suitably trained (including GCP training) medically qualified and delegated staff at each site. At each site the consent form was countersigned by the site PI. 2. We changed our protocol to record that we were storing stool and serum samples at -40 rather than -80 degrees C. 3. As recruitment was going more slowly than initially hoped, we requested an extension of the duration of the study beyond 31 Dec 2013.
15 July 2015	1. We minimally changed the inclusion criteria so that iron deficiency was defined now by a transferrin saturation of <18% rather than <16%. We had noticed at a monitoring visit at Chelsea and Westminster Hospital that they were using a version of the protocol showing 16% rather than 18%. 2. The faecal calprotectin assays were to be done in the routine Barts Health NHS Trust immunology laboratory rather than at Kings College Hospital (as originally planned) because the assay had now been established here as a routine clinical test. 3. The hepcidin assays were now to be undertaken in the Gastroenterology Laboratory at the University of Birmingham, under the supervision of Dr Tariq Iqbal, rather than here, because the Birmingham assay was well-established and probably the most reliable in the UK. 4. The letter to patients' GPs about their recruitment was very minimally modified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

For a description of the study's limitations, see the penultimate paragraph of the Discussion in the attached publication in Journal of Crohn's and Colitis, as well as Section 13 of the attached textual End of Trial Report.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27932449>